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(54) Title: ENDOGENOUS AND NON-ENDOGENOUS VERSIONS OF HUMAN G PROTEIN-COUPLED RECEPTORS

(57) Abstract: The invention disclosed in this patent docuemnt relates to transmembrane receptors, more particularly to a human G protein-coupled receptor and to mutated (non-endogenous) versions of the human GPCRs for evidence activity.

ENDOGENOUS AND NON-ENDOGENOUS VERSIONS OF HUMAN G PROTEIN-COUPLED RECEPTORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Serial Number 09/170,496, filed on October 13, 1998 and its corresponding PCT application number PCT/US99/23938, published as WO 00/22129 on April 20, 2000. This application also is a continuation in part of U.S. Ser. No. 09/060,188, filed April 14, 1998, which is a continuation in part of U.S. Ser. No. 08/839,449, filed April 14, 1997 (abandoned). The priority benefit of each of the foregoing is claimed herein, and the disclosures of each of the foregoing is incorporated by reference herein in its entirety. This application also claims the benefit of U.S. Provisional Number 60/271,913, filed February 26, 2001, also incorporated herein by reference in its entirety. This document is related to the following applications: U.S. Provisional Number 60/250,881, filed December 1, 2000; U.S. Provisional Number 60/253,428, filed November 27, 2000; U.S. Provisional Number 60/234,317, filed September 20, 2000; U.S. Provisional Number 60/245,853, filed November 3, 2000; U.S. Provisional Number 60/234,045, filed September 20, 2000; U.S. Provisional Number 60/200,568, filed April 28, 2000; U.S. Provisional Number 60/198,518, filed April 19, 2000; U.S. Provisional Number 60/189,353, filed March 14, 2000; U.S. Provisional Number 60/166,084, filed November 17, 1999; and U.S. Provisional Number 60/106,451, filed October 30, 1998, the disclosures of each of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to transmembrane receptors, in some embodiments to G protein-coupled receptors and, in some preferred embodiments, to endogenous GPCRs that are altered to establish or enhance constitutive activity of the receptor. In some embodiments, the constitutively activated GPCRs will be used for the direct identification of candidate compounds as receptor agonists or inverse agonists having applicability as therapeutic agents.

BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR) class. It is estimated that there are some 30,000-40,000 genes within the human genome, and of these, approximately 2% are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified, are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified are referred to as "orphan" receptors.

GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, approximately 60% of all prescription pharmaceuticals have been developed. For example, in 1999, of the top 100 brand name prescription drugs, the following drugs interact with GPCRs (diseases and/or disorders treated are indicated in parentheses):

Claritin® (allergies)	Prozac® (depression)	Vasotec® (hypertension)
Paxil® (depression)	Zoloft® (depression)	Zyprexa ® (psychotic disorder)
Cozaar® (hypertension)	Imitrex® (migraine)	Zantac® (reflux)
Propulsid® (reflux disease)	Risperdal® (schizophrenia)	Serevent® (asthma)
Pepcid® (reflux)	Gaster® (ulcers)	Atrovent® (bronchospasm)

Effexor® (depression)	Depakote® (epilepsy)	Cardura® (prostatic hypertrophy)
Allegra® (allergies)	Lupron® (prostate cancer)	Zoladex® (prostate cancer)
Diprivan® (anesthesia)	BuSpar® (anxiety)	Ventolin® (bronchospasm)
Hytrin® (hypertension)	Wellbutrin® (depression)	Zyrtec® (rhinitis)
Plavix® (MI/stroke)	Toprol-XL® (hypertension)	Tenormin® (angina)
Xalatan® (glaucoma)	Singulair® (asthma)	Diovan® (hypertension)
Harnal® (prostatic hyperplasia)		

(Med Ad News 1999 Data).

GPCRs share a common structural motif, having seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, *i.e.*, transmembrane-1 (TM-1), transmebrane-2 (TM-2), *etc.*). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the receptor lies in the extracellular space outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular "G-protein." It

has been reported that GPCRs are "promiscuous" with respect to G proteins, *i.e.*, that a GPCR can interact with more than one G protein. *See*, Kenakin, T., 43 *Life Sciences* 1095 (1988). Although other G proteins exist, currently, G_q, G_s, G_i, G_z and G_o are G proteins that have been identified. Ligand-activated GPCR coupling with the G-protein initiates a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. Although not wishing to be bound to theory, it is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to initiate signal transduction leading to a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response.

A receptor may be stabilized in an active state by a ligand or a compound such as a drug. Recent discoveries, including but not exclusively limited to modifications to the amino acid sequence of the receptor, provide means other than ligands or drugs to promote and stabilize the receptor in the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

SUMMARY OF THE INVENTION

Disclosed herein are endogenous and non-endogenous versions of human GPCRs and uses thereof.

Some embodiments of the present invention relate to a G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:2, non-endogenous, constitutively activated versions of the same encoded by an amino acid of SEQ.ID.NO.:63, and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:62 and host cells comprising the same.

Some embodiments of the present invention relate to a G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:4, non-endogenous, constitutively activated versions of the same encoded by an amino acid of SEQ.ID.NO.:65, and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:64 and host cells comprising the same.

Some embodiments of the present invention relate to G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:6, non-endogenous, constitutively activated versions of the same, and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:5 and host cells comprising the same.

Some embodiments of the present invention relate to a G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:8, non-endogenous, constitutively activated versions of the same encoded by an amino acid of SEQ.ID.NO.:67, SEQ.ID.NO.:69, SEQ.ID.NO.:71, and SEQ.ID.NO.:73, and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:66, SEQ.ID.NO.:68, SEQ.ID.NO.:70, and SEQ.ID.NO.:72, and host cells comprising the same.

Some embodiments of the present invention relate to a G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:10, non-endogenous, constitutively activated versions of the same encoded by an amino acid of SEQ.ID.NO.:75 and SEQ.ID.NO.:77, and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:74 and SEQ.ID.NO.:76, and host cells comprising the same.

Some embodiments of the present invention relate to a G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:12, non-endogenous, constitutively activated versions of the same encoded by an amino acid of SEQ.ID.NO.:79 and SEQ.ID.NO.:81, and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:78 and SEQ.ID.NO.:80, and host cells comprising the same.

Some embodiments of the present invention relate to a G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:14, constitutively activated versions of the same encoded by an amino acid of SEQ.ID.NO.:83, and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:82 and host cells comprising the same.

Some embodiments of the present invention relate to a G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:16, constitutively activated versions of the same encoded by an amino acid of SEQ.ID.NO.:85, and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:84 and host cells comprising the same.

Some embodiments of the present invention relate to a G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:18, constitutively activated versions of the same encoded by an amino acid of SEQ.ID.NO.:87, and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:86 and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:84 and host cells comprising the same.

Some embodiments of the present invention relate to a G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:98, non-endogenous, constitutively activated versions of the same and host cells comprising the same.

Some embodiments of the present invention relate to a plasmid comprising a vector and the cDNA of SEQ.ID.NO.:97 and host cells comprising the same.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphic representation of the results of a second messenger cell-based cyclic AMP assay providing comparative results for constitutive signaling of endogenous, constitutively active FPRL-2 ("FPRL-2 wt"), non-endogenous, constitutively activated

version of FPRL-2 ("FPRL-2 (L240K)") fused with a Gs/Gi Fusion Protein Construct and a control ("Gs/Gi").

Figure 2 provides graphic results of comparative analysis of endogenous STRL33 against non-endogenous, constitutively activated STRL33 ("STRL33(L230K)") utilizing an 8XCRE-Luc Reporter assay in 293T cells as compared with the control ("CMV").

Figure 3 provides graphic results of comparative analysis of a co-transfection of non-endogenous TSHR(A623I) ("signal enhancer") with an endogenous target receptor, in this case GPR45 ("GPR45 wt"), versus a control ("CMV"), utilizing a cell-based adenylyl cyclase assay in 293 cells. This assay involved the addition of TSH, the endogenous ligand for TSHR.

Figure 4 provides graphic results of comparative analysis of a co-transfection of non-endogenous TSHR(A623I) ("signal enhancer") and an endogenous target receptor, in this case mGluR7 ("mGluR7 wt"), versus non-endogenous, constitutively activated versions of the target receptor mGluR7 ("W590S," "R659H" "T771C" and "I790K") co-transfected with non-endogenous TSHR(A623I), utilizing a cell-based adenylyl cyclase assay in 293 cells. This assay involved the addition of TSH, the endogenous ligand for TSHR.

Figure 5 provides graphic results of comparative analysis of a co-transfection of non-endogenous TSHR(A623I) ("signal enhancer") and an endogenous target receptor, in this case mGluR7 ("mGluR7 wt"), versus non-endogenous, constitutively activated versions of the target receptor mGluR7 ("W590S," "R659H" "T771C" and "I790K") co-transfected with non-endogenous TSHR(A623I), utilizing a cell-based adenylyl cyclase assay in RGT cells. This assay involved the addition of TSH, the endogenous ligand for TSHR.

Figure 6 provides an illustration of second messenger IP_3 production of non-endogenous mGluR7, "T771C", co-transfected with non-endogenous versions of Gq

protein, "Gq(del)" and "Gq(del)/Gi" compared with "Gq(del)" and "Gq(del)/Gi" in the presence and absence of glutamate.

Figure 7 is a comparative analysis of endogenous, non-constitutively active GPR37 ("wt") and non-endogenous, constitutively activated versions of GPR37 ("C543Y" and "L352R") in an SRE Reporter assay, where the control is expression vector ("CMV").

Figure 8 is comparative analysis of a co-transfection of Gs/Gi Fusion Construct and an endogenous target receptor, in this case GPR37 ("GPR37 wt"), versus non-endogenous, constitutively activated versions of the target receptor GPR37 ("C543Y" and "L352R") co-transfected with Gs/Gi Fusion Construct utilizing a whole cell second messenger cAMP assay.

Figure 9 is a representation of a Northern Analysis of GPR37 expressed in forskolin treated rat Schwann cells. Cell differentiation was maintained at 20uM of forskolin.

Figure 10 is a representation of a Northern Analysis of GPR37 expressed in crushed rat sciatic nerve. GPR37 was highly up-regulated seven (7) days post crush.

Figure 11 is a comparative analysis of endogenous, non-constitutively active HF1948 ("wt") and non-endogenous, constitutively activated version of HF1948 ("I281F") in an IP3 assay, where the control is expression vector ("pCMV").

Figure 12 is comparative analysis of a co-transfection of non-endogenous TSHR-A623I ("signal enhancer") and an endogenous target receptor, in this case HF1948 ("HF1948 wt"), versus non-endogenous, constitutively activated versions of the target receptor HF1948 ("I281F" and "E135N") co-transfected with non-endogenous TSHR-A623I, utilizing a whole cell adenylyl cyclase assay. This assay involved the addition of TSH, the endogenous ligand for TSHR.

Figure 13 a reproduction of a photograph of the results for the Northern Blot of GPR66 using multiple pancreatic cell lines.

Figure 14 provides graphic results of comparative analysis of endogenous GPR35 against non-endogenous, constitutively activated GPR35 ("GPR35(A216K)") utilizing an E2F-Luc Reporter assay in 293A cells.

Figure 15 is a reproduction of a photograph of the results for the Northern Blot of GPR35 using multiple tissue (human) cDNA.

Figures 16 provides graphic results of comparative analysis of a co-transfection of non-endogenous TSHR-A623I ("TSHR-A623I") (with and without TSH) and endogenous ETBR-LP2 ("WT"), versus non-endogenous, constitutively activated ETBR-LP2 ("N358K") co-transfected with mutated TSHR-A623I (with and without TSH) utilizing an adenylyl cyclase assay.

Figure 17 provides a graphic result comparative analysis of endogenous ETBR-LP2 ("WT") and non-endogenous, constitutively activated ETBR-LP2 ("N358K") utilizing an AP1 reporter assay system.

Figure 18 is a representation of a Northern Analysis of ETBR-LP2 expressed in forskolin treated rat Schwann cells. Cell differentiation was maintained at 20uM of forskolin.

Figure 19 is a representation of a Northern Analysis of ETBR-LP2 expressed in crushed rat sciatic nerve. ETBR-LP2 was highly up-regulated seven (7) days post crush.

Figures 20A and 20B provides an alignment report between the putative amino acid sequence of the human ETBR-LP2 ("hETBRLP2p") and the reported amino acid sequence of human GPR37 ("hGPR37p").

DETAILED DESCRIPTION

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

AGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes. In some embodiments, **AGONISTS** are those materials not previously known to activate the intracellular response when they bind to the receptor or to enhance GTP binding to membranes.

AMINO ACID ABBREVIATIONS used herein are set out in Table A:

TABLE A

ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K

METHIONINE	MET	M
PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

ANTAGONIST shall mean materials (*e.g.*, ligands, candidate compounds) that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists. ANTAGONISTS do not diminish the baseline intracellular response in the absence of an agonist. In some embodiments, ANTAGONISTS are those materials not previously known to activate the intracellular response when they bind to the receptor or to enhance GTP binding to membranes.

CANDIDATE COMPOUND shall mean a molecule (for example, and not limitation, a chemical compound) that is amenable to a screening technique. Preferably, the phrase "candidate compound" does not include compounds which were publicly known to be compounds selected from the group consisting of inverse agonist, agonist or antagonist to a receptor, as previously determined by an indirect identification process ("indirectly identified compound"); more preferably, not including an indirectly identified compound which has previously been determined to have therapeutic efficacy in at least one mammal; and, most preferably, not including an indirectly identified compound which has previously been determined to have therapeutic utility in humans.

COMPOSITION means a material comprising at least one component; a "pharmaceutical composition" is an example of a composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality; i.e. the ability to activate/inhibit a signal transduction pathway, as opposed to receptor binding affinity. Exemplary means of detecting compound efficacy are disclosed in the Example section of this patent document.

CODON shall mean a grouping of three nucleotides (or equivalents to nucleotides) which generally comprise a nucleoside (adenosine (A), guanosine (G), cytidine (C), uridine (U) and thymidine (T)) coupled to a phosphate group and which, when translated, encodes an amino acid.

CONSTITUTIVELY ACTIVATED RECEPTOR shall mean a receptor subjected to constitutive receptor activation. A constitutively activated receptor can be endogenous or non-endogenous.

CONSTITUTIVE RECEPTOR ACTIVATION shall mean stabilization of a receptor in the active state by means other than binding of the receptor with its ligand or a chemical equivalent thereof.

CONTACT or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

DIRECTLY IDENTIFYING or **DIRECTLY IDENTIFIED**, in relationship to the phrase "candidate compound", shall mean the screening of a candidate compound against a constitutively activated receptor, preferably a constitutively activated orphan receptor, and most preferably against a constitutively activated G protein-coupled cell surface orphan receptor, and assessing the compound efficacy of such compound. This

phrase is, under no circumstances, to be interpreted or understood to be encompassed by or to encompass the phrase "indirectly identifying" or "indirectly identified."

ENDOGENOUS shall mean a material that a mammal naturally produces. ENDOGENOUS in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus. By contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For example, and not limitation, in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

G PROTEIN COUPLED RECEPTOR FUSION PROTEIN and **GPCR FUSION PROTEIN**, in the context of the invention disclosed herein, each mean a non-endogenous protein comprising an endogenous, constitutively activate GPCR or a non-endogenous, constitutively activated GPCR fused to at least one G protein, most preferably the alpha (α) subunit of such G protein (this being the subunit that binds GTP), with the G protein preferably being of the same type as the G protein that naturally couples with endogenous orphan GPCR. For example, and not limitation, in an endogenous state, if the G protein "$G_s\alpha$" is the predominate G protein that couples with the GPCR, a GPCR Fusion

Protein based upon the specific GPCR would be a non-endogenous protein comprising the GPCR fused to $G_s\alpha$; in some circumstances, as will be set forth below, a non-predominant G protein can be fused to the GPCR. The G protein can be fused directly to the C-terminus of the constitutively active GPCR or there may be spacers between the two.

HOST CELL shall mean a cell capable of having a Plasmid and/or Vector incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as a autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. In some embodiments the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

INDIRECTLY IDENTIFYING or **INDIRECTLY IDENTIFIED** means the traditional approach to the drug discovery process involving identification of an endogenous ligand specific for an endogenous receptor, screening of candidate compounds against the receptor for determination of those which interfere and/or compete with the ligand-receptor interaction, and assessing the efficacy of the compound for affecting at least one second messenger pathway associated with the activated receptor.

INHIBIT or **INHIBITING**, in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INVERSE AGONISTS shall mean materials (*e.g.*, ligand, candidate compound) which bind to either the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the

active form of the receptor below the normal base level of activity which is observed in the absence of agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and most preferably at least 99% as compared with the baseline response in the absence of the inverse agonist.

KNOWN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has been identified.

LIGAND shall mean a molecule specific for a naturally occurring receptor.

MUTANT or **MUTATION** in reference to an endogenous receptor's nucleic acid and/or amino acid sequence shall mean a specified change or changes to such endogenous sequences such that a mutated form of an endogenous, non-constitutively activated receptor evidences constitutive activation of the receptor. In terms of equivalents to specific sequences, a subsequent mutated form of a human receptor is considered to be equivalent to a first mutation of the human receptor if (a) the level of constitutive activation of the subsequent mutated form of a human receptor is substantially the same as that evidenced by the first mutation of the receptor; and (b) the percent sequence (amino acid and/or nucleic acid) homology between the subsequent mutated form of the receptor and the first mutation of the receptor is at least 80%, at least 85%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and most preferably at least 99%. In some embodiments, owing to the fact that some preferred cassettes disclosed herein for achieving constitutive activation include a single amino acid and/or codon change between the

endogenous and the non-endogenous forms of the GPCR, it is preferred that the percent sequence homology should be at least 98%.

NON-ORPHAN RECEPTOR shall mean an endogenous naturally occurring molecule specific for an identified ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

ORPHAN RECEPTOR shall mean an endogenous receptor for which the ligand specific for that receptor has not been identified or is not known.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

SECOND MESSENGER shall mean an intracellular response produced as a result of receptor activation. A second messenger can include, for example, inositol triphosphate (IP_3), diacycglycerol (DAG), cyclic AMP (cAMP), and cyclic GMP (cGMP). Second messenger response can be measured for a determination of receptor activation. In addition, second messenger response can be measured for the direct identification of candidate compounds, including for example, inverse agonists, agonists, and antagonists.

SIGNAL TO NOISE RATIO shall mean the signal generated in response to activation, amplification, or stimulation wherein the signal is above the background noise or the basal level in response to non-activation, non-amplification, or non-stimulation.

SPACER shall mean a translated number of amino acids that are located after the last codon or last amino acid of a gene, for example a GPCR of interest, but before the start codon or beginning regions of the G protein of interest, wherein the translated number amino acids are placed in-frame with the beginnings regions of the G protein of interest. The number of translated amino acids can be tailored according to the needs of the skilled artisan and is generally from about one amino acid, preferably two amino acids, more preferably three amino acids, more preferably four amino acids, more preferably five amino acids, more preferably six amino acids, more preferably seven amino acids, more preferably eight amino acids, more preferably nine amino acids, more preferably ten amino acids, more preferably eleven amino acids, and even more preferably twelve amino acids.

STIMULATE or **STIMULATING**, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

SUBSTANTIALLY shall refer to a result which is within 40% of a control result, preferably within 35%, more preferably within 30%, more preferably within 25%, more preferably within 20%, more preferably within 15%, more preferably within 10%, more preferably within 5%, more preferably within 2%, and most preferably within 1% of a control result. For example, in the context of receptor functionality, a test receptor may exhibit substantially similar results to a control receptor if the transduced signal, measured using a method taught herein or similar method known to the art-skilled, if within 40% of the signal produced by a control signal.

VECTOR in reference to cDNA shall mean a circular DNA capable of incorporating at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

A. Introduction

The traditional study of receptors has typically proceeded from the *a priori* assumption (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized is that it is the active state of the receptor that is most useful for discovering agonists and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand. This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

B. Identification of Human GPCRs

The efforts of the Human Genome project have led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins. Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art.

Receptor homology is useful in terms of gaining an appreciation of a role of the receptors within the human body. As the patent document progresses, techniques for mutating these receptors to establish non-endogenous, constitutively activated versions of these receptors will be discussed.

The techniques disclosed herein are also applicable to other human GPCRs known to the art, as will be apparent to those skilled in the art.

C. Receptor Screening

Screening candidate compounds against a non-endogenous, constitutively activated version of the GPCRs disclosed herein allows for the direct identification of candidate compounds which act at the cell surface receptor, without requiring use of the receptor's endogenous ligand. Using routine, and often commercially available techniques, one can determine areas within the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed. The expression location of a receptor in a specific tissue provides a scientist with the ability to assign a physiological functional role of the receptor. It is also possible using these techniques to determine related disease/disorder states which are associated with the expression and/or over-expression of the receptor; such an approach is disclosed in this patent document. Furthermore,

expression of a receptor in diseased organs can assist one in determining the magnitude of the clinical relevance of the receptor.

Constitutive activation of the GPCRs disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR; this algorithmic technique is disclosed in co-pending and commonly assigned patent document PCT Application Number PCT/US99/23938, published as WO 00/22129 on April 20, 2000, which, along with the other patent documents listed herein, is incorporated herein by reference in its entirety. The algorithmic technique is not predicated upon traditional sequence "alignment" but rather a specified distance from the aforementioned TM6 proline residue (or, of course, endogenous constitutive substitution for such proline residue). By mutating an amino acid of residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue, constitutive activation of the receptor may be obtained. Other amino acid residues may be useful in the mutation at this position to achieve this objective.

D. Disease/Disorder Identification and/or Selection

As will be set forth in greater detail below, inverse agonists and agonists to the non-endogenous, constitutively activated GPCR can be identified by the methodologies of this invention. Such inverse agonists and agonists are ideal candidates as lead compounds in drug discovery programs for treating diseases related to this receptor. Because of the ability to directly identify inverse agonists to the GPCR, thereby allowing for the development of pharmaceutical compositions, a search for diseases and disorders associated with the GPCR is relevant. The expression location of a receptor in a specific tissue provides a scientist with the ability to assign a physiological function to the receptor. For example, scanning both diseased and normal tissue samples for the presence of the GPCR now becomes more

than an academic exercise or one which might be pursued along the path of identifying an endogenous ligand to the specific GPCR. Tissue scans can be conducted across a broad range of healthy and diseased tissues. Such tissue scans provide a potential first step in associating a specific receptor with a disease and/or disorder. Furthermore, expression of a receptor in diseased organs can assist one in determining the magnitude of clinical relevance of the receptor. Skilled artisans, armed with the present specification, are credited with the ability to infer the function of a GPCR once the receptor is localized to a certain tissue or region.

The DNA sequence of the GPCR can be used to make a probe/primer. In some preferred embodiments the DNA sequence is used to make a probe for (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of the expression of the receptor in tissue samples. The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be used to correlate location to function and indicate the receptor's physiological role/function and create a treatment regimen, including but not limited to, a disease associated with that function/role. Receptors can also be localized to regions of organs by this technique. Based on the known or assumed roles/functions of the specific tissues to which the receptor is localized, the putative physiological function of the receptor can be deduced. For example and not limitation, proteins located/expressed in areas of the thalamus are associated with sensorimotor processing and arousal (*see*, Goodman & Gilman's, The Pharmacological Basis of Therapeutics, 9th Edition, page 465 (1996)). Proteins expressed in the hippocampus or in Schwann cells are associated with learning and memory, and myelination of peripheral nerves, respectively (*see*, Kandel, E. et al., Essentials of Neural Science and Behavior pages 657, 680 and 28, respectively (1995)). In

some embodiments, the probes and/or primers may be used to detgect and/or diagnose diseases and/or disorders, including but not limited to, those diseases and disorders identified in Example 6, *infra*. Methods of generating such primers and/or probes are well known to those of skill in the art as well as methods of using primers and/or probes to detect diseases and/or disorders.

E. Screening of Candidate Compounds

1. Generic GPCR screening assay techniques

When a G protein receptor becomes constitutively active, it binds to a G protein (*e.g.*, G_q, G_s, G_i, G_z, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, [^{35}S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that [^{35}S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The use of this assay system is typically for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

2. Specific GPCR screening assay techniques

Once candidate compounds are identified using the "generic" G protein-coupled receptor assay (*i.e.*, an assay to select compounds that are agonists or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is

preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

a. G_s, G_z and G_i.

G_s stimulates the enzyme adenylyl cyclase. G_i (and G_z and Go), on the other hand, inhibits adenylyl cyclase. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, constitutively activated GPCRs that couple the G_s protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple G_i (or G_z, Go) protein are associated with decreased cellular levels of cAMP. *See, generally*, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to the receptor (*i.e.*, such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription factor (CREB) that then binds to the promoter at specific sites (cAMP response elements) and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, *e.g.*, β-galactosidase or luciferase. Thus, a constitutively activated G_s-linked receptor causes the accumulation of cAMP that then activates the gene and leads to the expression of the reporter protein. The reporter protein

such as β-galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

b. G_o and G_q

G_q and G_o are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP_2, releasing two intracellular messengers: diacycloglycerol (DAG) and inositol 1,4,5-triphoisphate (IP_3). Increased accumulation of IP_3 is associated with activation of G_q- and Go-associated receptors. *See, generally*, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Assays that detect IP_3 accumulation can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to a G_q- or Go-associated receptor (*i.e.*, such a compound would decrease the levels of IP_3). G_q-associated receptors can also be examined using an AP1 reporter assay wherein G_q-dependent phospholipase C causes activation of genes containing AP1 elements; thus, activated G_q-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will evidence an increase in such expression. Commercially available assays for such detection are available.

3. GPCR Fusion Protein

The use of an endogenous, constitutively activated GPCR or a non-endogenous, constitutively activated GPCR, for use in screening of candidate compounds for the direct identification of inverse agonists, agonists provide an interesting screening challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, in order to differentiate between, *e.g.*, the non-endogenous receptor in the presence of a candidate compound and the non-endogenous receptor in the absence of that

compound, with an aim of such a differentiation to allow for an understanding as to whether such compound may be an inverse agonist or agonist or have no affect on such a receptor, it is preferred that an approach be utilized that can enhance such differentiation. A preferred approach is the use of a GPCR Fusion Protein.

Generally, once it is determined that a non-endogenous GPCR has been constitutively activated using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR. Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. In some embodiments it is preferred that screening take place using a mammalian expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the non-endogenous, constitutively activated GPCR will continuously signal. In some embodiments it is preferred that this signal be enhanced such that in the presence of, *e.g.*, an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling with the non-endogenous GPCR. The GPCR Fusion Protein is preferred for screening with either an endogenous, constitutively active GPCR or a non-endogenous, constitutively activated GPCR because such an approach increases the signal that is utilized in such screening techniques. This is important in facilitating a significant "signal to noise" ratio; such a significant ratio is preferred for the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available

expression vectors and systems offer a variety of approaches that can fit the particular needs of an investigator. Important criteria on the construction of such a GPCR Fusion Protein construct include but are not limited to, that the endogenous GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the endogenous GPCR is upstream of the G protein sequence), and that the "stop" codon of the GPCR be deleted or replaced such that upon expression of the GPCR, the G protein can also be expressed. Other embodiments include constructs wherein the endogenous GPCR sequence and the G protein sequence are not in-frame and/or the "stop" codon is not deleted or replaced. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12, although this number can be readily ascertained by one of ordinary skill in the art). Based upon convenience it is preferred to use a spacer. Preferably, the G protein that couples to the non-endogenous GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been identified, it is preferred that a construct comprising the sequence of the G protein (*i.e.*, a universal G protein construct (see *Examples*)) be available for insertion of an endogenous GPCR sequence therein; this provides for further efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

As noted above, constitutively activated GPCRs that couple to G_i, G_z and G_o are expected to inhibit the formation of cAMP making assays based upon these types of GPCRs challenging (*i.e.*, the cAMP signal decreases upon activation thus making the direct identification of, *e.g.*, inverse agonists (which would further decrease this signal), challenging. As will be disclosed herein, we have ascertained that for these types of receptors, it is possible to create a GPCR Fusion Protein that is not based upon the GPCRs

endogenous G protein, in an effort to establish a viable cyclase-based assay. Thus, for example, an endogenous G_i coupled receptor can be fused to a G_s protein –such a fusion construct, upon expression, "drives" or "forces" the endogenous GPCR to couple with, *e.g.*, G_s rather than the "natural" G_i protein, such that a cyclase-based assay can be established. Thus, for G_i, G_z and G_o coupled receptors, in some embodiments it is preferred that when a GPCR Fusion Protein is used and the assay is based upon detection of adenylyl cyclase activity, that the fusion construct be established with G_s (or an equivalent G protein that stimulates the formation of the enzyme adenylyl cyclase).

G protein	**Effect of cAMP Production upon Activation of GPCR (*i.e.*, constitutive activation or agonist binding)**	**Effect of IP_3 Accumulation upon Activation of GPCR (*i.e.*, constitutive activation or agonist binding)**	**Effect of cAMP Production upon contact with an Inverse Agonist**	**Effect on IP_3 Accumulation upon contact with an Inverse Agonist**
G_s	Increase	N/A	Decrease	N/A
G_i	Decrease	N/A	Increase	N/A
G_z	Decrease	N/A	Increase	N/A
Go	Decrease	Increase	Increase	Decrease
G_q	N/A	Increase	N/A	Decrease

Equally effective is a G Protein Fusion construct that utilizes a G_q Protein fused with a G_s, G_i, G_z or G_o Protein. In some embodiments a preferred fusion construct can be accomplished with a G_q Protein wherein the first six (6) amino acids of the G-protein α-subunit ("Gαq") is deleted and the last five (5) amino acids at the C-terminal end of Gαq is replaced with the corresponding amino acids of the Gα of the G protein of interest. For example, a fusion construct can have a G_q (6 amino acid deletion) fused with a G_i Protein, resulting in a "G_q/G_i Fusion Construct". This fusion construct will forces the endogenous G_i coupled receptor to couple to its non-endogenous G protein, G_q, such that the second

messenger, for example, inositol triphosphate or diacylgycerol, can be measured *in lieu* of cAMP production.

4. Co-transfection of a Target G_i Coupled GPCR with a Signal-Enhancer G_s Coupled GPCR (cAMP Based Assays)

A G_i coupled receptor is known to inhibit adenylyl cyclase, and, therefore, decreases the level of cAMP production, which can make assessment of cAMP levels challenging. An effective technique in measuring the decrease in production of cAMP as an indication of constitutive activation of a receptor that predominantly couples G_i upon activation can be accomplished by co-transfecting a signal enhancer, *e.g.,* a non-endogenous, constitutively activated receptor that predominantly couples with G_s upon activation (*e.g.*, TSHR-A623I, disclosed below), with the G_i linked GPCR. As is apparent, constitutive activation of a G_s coupled receptor can be determined based upon an increase in production of cAMP. Constitutive activation of a G_i coupled receptor leads to a decrease in production cAMP. Thus, the co-transfection approach is intended to advantageously exploit these "opposite" affects. For example, co-transfection of a non-endogenous, constitutively activated G_s coupled receptor (the "signal enhancer") with the endogenous G_i coupled receptor (the "target receptor") provides a baseline cAMP signal (*i.e.,* although the G_i coupled receptor will decrease cAMP levels, this "decrease" will be relative to the substantial increase in cAMP levels established by constitutively activated G_s coupled signal enhancer). By then co-transfecting the signal enhancer with a constitutively activated version of the target receptor, cAMP would be expected to further decrease (relative to base line) due to the increased functional activity of the G_i target (*i.e.*, which decreases cAMP).

Screening of candidate compounds using a cAMP based assay can then be accomplished, with two 'changes' relative to the use of the endogenous receptor/G-protein fusion: first, relative to the G_i coupled target receptor, "opposite" effects will result, *i.e.,* an

inverse agonist of the G_i coupled target receptor will increase the measured cAMP signal, while an agonist of the G_i coupled target receptor will decrease this signal; second, as would be apparent, candidate compounds that are directly identified using this approach should be assessed independently to ensure that these do not target the signal enhancing receptor (this can be done prior to or after screening against the co-transfected receptors).

F. Medicinal Chemistry

Generally, but not always, direct identification of candidate compounds is conducted in conjunction with compounds generated via combinatorial chemistry techniques, whereby thousands of compounds are randomly prepared for such analysis. Generally, the results of such screening will be compounds having unique core structures; thereafter, these compounds may be subjected to additional chemical modification around a preferred core structure(s) to further enhance the medicinal properties thereof. Such techniques are known to those in the art and will not be addressed in detail in this patent document.

G. Pharmaceutical compositions

Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers are available to those in the art; for example, see Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Osol et al., eds.).

H. Other Utilities

Although a preferred use of the non-endogenous versions of the GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse agonists or agonists (preferably for use as pharmaceutical agents), other uses of these versions of GPCRs exist. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling cascade. In some embodiments it is preferred that the endogenous receptors be "orphan receptors", *i.e.*, the endogenous ligand for the receptor has not been identified. In some embodiments, therefore, the modified, non-endogenous GPCRs can be used to understand the role of endogenous receptors in the human body before the endogenous ligand therefore is identified. Such receptors can also be used to further elucidate known receptors and the pathways through which they transduce a signal. Other uses of the disclosed receptors will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. The traditional approach to application or understanding of sequence cassettes from one sequence to another (*e.g.* from rat receptor to human receptor or from human receptor A to human receptor B) is generally predicated upon sequence alignment techniques whereby the sequences are aligned in an effort to determine areas of

commonality. The mutational approach disclosed herein does not rely upon this approach but is instead based upon an algorithmic approach and a positional distance from a conserved proline residue located within the TM6 region of human GPCRs. Once this approach is secured, those in the art are credited with the ability to make minor modifications thereto to achieve substantially the same results (*i.e.*, constitutive activation) disclosed herein. Such modified approaches are considered within the purview of this disclosure.

Example 1
ENDOGENOUS HUMAN GPCRS

The following cDNA receptors were cloned by utilizing the techniques in this Section, see below. Table B lists the receptors disclosed throughout this patent applications, the open reading frame, the nucleic acid and the amino acid sequences for the endogenous GPCR (Table B).

TABLE B

Disclosed Human GPCRs	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID. NO.	Amino Acid SEQ.ID.NO.
FPRL-2	1,062bp	1	2
STLR33	1,029bp	3	4
GPR45	1,119bp	5	6
mGluR7	2,748bp	7	8
GPR37	1,842bp	9	10
HF1948	1,086bp	11	12
GPR66	957bp	13	14
GPR35	930bp	15	16
ETBR-LP2	1,446bp	17	18
GPR26	1,011	97	98

2. Full Length Cloning Protocol

a. FPRL-2 (Seq. Id. Nos. 1 & 2)

FPRL-2 was cloned and sequenced in 1992. Bao, L. et al., 13(2) *Genomics* 437-40 (1992). FPRL-2 has been reported to be located on chromosome 19 having a sequence similarity to N-formy peptide receptor like-1 (FPRL-1) both of which share significant similarity with the N-formyl peptide receptor (FPR). The endogenous ligand for FPR is formyl peptide, however, the two homologues of FPR, FPRL-1 and FPRL-2, do not bind to the same ligand but are likely chemotactic receptors. 13(2) *Genomics* 437-40 (1992). Chemotactic receptors are reported to be involved in inflammation. FPRL-2 is a GPCR having an open reading frame of 1062 bp encoding a 353 amino acid protein.

PCR was performed using genomic cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 64°C for 1 min 20 sec and 72°C for 2 min. The 5' PCR contained an EcoRI site with the following sequence

5'-AAAGATTCAGGTGTGGGAAGATGGAAACC-3' (SEQ.ID.NO.:19)

and the 3' primer contained an ApaI site with the following sequence:

5'-AAAGGATCCCCGACCTCACATTGCTTGTA -3' (SEQ.ID.NO.:20).

The PCR fragment was digested with EcoRI and ApaI and cloned into an EcoRI-ApaI site of CMV expression vector. Nucleic acid (SEQ.ID.NO.:1) and amino acid (SEQ.ID.NO.:2) sequences for human FPRL-2 were thereafter determined and verified.

b. STLR33 (Seq. Id. Nos. 3 & 4)

PCR was performed using genomic cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C

for 1 min, 62°C for 1 min 20 sec and 72°C for 2 min. The 5' PCR contained an EcoRI site with the following sequence

5'-CAGGAATTCATCAGAACAGACACCATGGCA-3' (SEQ.ID.NO.:21)

and the 3' primer contained a BamHI site with the following sequence:

5'-GCAGGATCCAGAGCAGTTTTTTCGAAACCCT -3' (SEQ.ID.NO.:22).

The PCR fragment was digested with EcoRI and BamHI and cloned into an EcoRI-BamHI site of CMV expression vector. Nucleic acid (SEQ.ID.NO.:3) and amino acid (SEQ.ID.NO.:4) sequences for human STRL33 were thereafter determined and verified.

c. GPR45 (Seq. Id. Nos. 5 & 6)

PCR was performed using genomic cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was as follows with cylces 2 through four repeated 35 times: 96°C for 2 min, 96°C for 30 sec, 55°C for 20 sec. 72°C for 1 min and 20 sec, and 72°C for 5 min. The 5' PCR contained a HindIII site with the following sequence

5'-TCCAAGCTTCAAGGGTCTCTCCACGATGGCCTG-3' (SEQ.ID.NO.:23)

and the 3' primer contained an EcoRI site with the following sequence:

5'-TGCGAATTCTCTGTGGCCCCCTGACCCCCTAAA -3' (SEQ.ID.NO.:24).

The PCR fragment was digested with HindIII and EcoRI and cloned into a HindIII-EcoRI site of CMV expression vector. Nucleic acid (SEQ.ID.NO.:5) and amino acid (SEQ.ID.NO.:6) sequences for human GPR45 were thereafter determined and verified.

The cDNA was then tagged with V5 by resubcloning into V5-His vector using pfu PCR and the following two primers utilized had the following sequence: 5'-GGTAAGCTTACCATGGCCTGCAACAGCACGTCCCTT-3' (SEQ.ID.NO.:25) and 5'-GACGAATTCAACCGCAGACTGGTTTTCATTGCA-3' (SEQ.ID.NO.:26).

The cycle condition was 30 cycles of 94°C for 1 min, 60°C for 2min and 72°C for 2 min.

d. mGLUR7 (Seq. Id. Nos. 7 & 8)

Glutamate is an excitatory neurotransmitter which is abundantly found in the mammalian brain. *See*, Dingledine, R. et al., 130(4S Suppl) J Nutr. 1039S (2000). There are two classes of glutamate receptor, the ionotropic (ligand-gated ion channels) and the metabotropic (GPCRs). Metabotropic glutamate receptors are a heterogenous family of GPCRs that are linked to several second messenger pathways to regulate neuronal excitability and synaptic transmission. (*See*, Phillips, T. et al., 57(1) Brain Res Mol Brain Res 132 (1998)). Metabotropic glutamate receptor type 7 (mGluR7) has been reported to be expressed in the brain, with highest levels of expression found in the hippocampus, cerebral cortex and cerebellum. *See,* Makoff, A. et al., 40(1) Brain Res Mol Brain Res 165 (1996). Based on the areas of the brain in which the receptor is localized, the putative functional role of the receptor can be deduced. For example, and while not wishing to be bound by any particular theory, mGluR7 is thought to play a role in depression, anxiety, obesity, Alzheimer's Disease, pain and stroke.

mGluR7 cDNA was generously supplied by Elizabeth Hoffman, Ph.D. The vector utilized for mGluR7 was pRcCMV (the coding region for mGluR7 was subcloned into pCMV vector at an EcoRI-ClaI site). *See,* SEQ.ID.NO.:7 for nucleic acid sequence and SEQ.ID.NO.:8 for the deduced amino acid sequence of mGluR7.

e. GPR37 (Seq. Id. Nos. 9 & 10)

The present invention also relates to the human GPR37. GPR37 was cloned and sequenced in 1997. Marazziti, D. et al., 45 (1) *Genomics* 68-77 (1997). GPR37 is an orphan GPCR having an open reading frame of 1839 bp encoding a 613 amino acid protein. GPR37 has been reported to share homology with the endothelin type B-like receptor and expressed in the human brain tissues, particularly in corpus callosum, medulla, putamen, and caudate nucleus.

PCR was performed using brain cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 62°C for 1min and 72°C for 2 min. The 5' PCR contained a HindIII site with the following sequence

5'-GCAAGCTTGTGCCCTCACCAAGCCATGCGAGCC-3' (SEQ.ID.NO.:27)

and the 3' primer contained an EcoRI site with the following sequence:

5'-CGGAATTCAGCAATGAGTTCCGACAGAAGC -3' (SEQ.ID.NO.:28).

The 1.9 kb PCR fragment was digested with HindIII and EcoRI and cloned into a HindIII-EcoRI site of CMVp expression vector. Nucleic acid (SEQ.ID.NO.:9) and amino acid (SEQ.ID.NO.:10) sequences for human GPR37 were thereafter determined and verified.

f. HF1948 (Seq. Id. Nos. 11 & 12)

HF1948 cDNA was generously supplied by Elizabeth Hoffman, Ph.D. The vector utilized for HF1948 was pRcCMV (the coding region for HF1948 was subcloned into pCMV vector at an HindIII-BamHI site). *See,* SEQ.ID.NO.:11 for nucleic acid sequence and SEQ.ID.NO.:12 for the deduced amino acid sequence of HF1948.

g. GPR66 (Seq. Id. Nos. 13 & 14)

The cDNA for human GPR66 (GenBank Accession Numbers AF044600 and AF044601) was generated and cloned into pCMV expression vector as follows: PCR was performed using genomic DNA as template and TaqPlus Precision polymerase (Stratagene) for first round PCR or pfu polymerase (Stratagene) for second round PCR with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM (TaqPlus Precision) or 0.5 mM (pfu) of each of the 4 nucleotides. When pfu was used, 10% DMSO was included in the buffer. The cycle condition was 30 cycles of: 94°C for 1 min; 65°C for 1min; and 72°C for: (a) 1 min for first round PCR; and (b) 2 min for second round PCR. Because there is an intron in the coding region, two sets of primers were separately used to generate overlapping 5' and 3' fragments. The 5' fragment PCR primers were:

5'-ACCATGGCTTGCAATGGCAGTGCGGCCAGGGGGCACT-3' (external sense) (SEQ.ID.NO.:29) and

5'-CGACCAGGACAAACAGCATCTTGGTCACTTGTCTCCGGC-3'(internal antisense) (SEQ.ID.NO.:30).

The 3' fragment PCR primers were:

5'-GACCAAGATGCTGTTTGTCCTGGTCGTGGTGTTTGGCAT-3' (internal sense) (SEQ.ID.NO.:31) and

5'-CGGAATTCAGGATGGATCGGTCTCTTGCTGCGCCT-3' (external antisense with an EcoRI site) (SEQ.ID.NO.:32).

The 5' and 3' fragments were ligated together by using the first round PCR as template and the kinased external sense primer and external antisense primer to perform second round PCR. The 1.2 kb PCR fragment was digested with EcoRI and cloned into the blunt-EcoRI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.:13) and amino

acid (SEQ.ID.NO.:14) sequences for human GPR66 were thereafter determined and verified.

h. GPR35 (Seq. Id. Nos. 15 & 16)

GPR35 is a 309 amino acid sequence whereby the endogenous ligand for GPR35 is unknown (O'Dowd B. et al., 47(2) Genomics 310 (1998)). GPR35 was determined to interact with a specific transcription factor, known as E2F, which is necessary for initiating DNA replication and, ultimately, cell proliferation. Within a cell, E2F couples to a tumor suppressor gene, known as retino-blastoma ("Rb"). Upon phosphorylation of this transcription factor construct, E2F is liberated from the Rb gene and then enters the nucleus of the cell. Inside the nucleus, E2F binds to genes, such as DNA polymerase, to initiate DNA replication, which results in proliferation of the cell.

PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 62°C for 1min and 72 °C for 1 min and 20 sec. The 5' PCR primer was kinased with the following sequence:

5'-GCGAATTCCGGCTCCCTGTGCTGCCCCAGG-3' (SEQ.ID.NO.:33)

and the 3' primer contains a BamHI site with the following sequence:

5'-GCGGATCCCGGAGCCCCCGAGACCTGGCCC -3' (SEQ.ID.NO.:34).

The 1 kb PCR fragment was digested with BamHI and cloned into EcoRV-BamHI site of CMVp expression vector. All 6 clones sequenced contain a potential polymorphism involving change of amino acid 294 from Arg to Ser. Nucleic acid (SEQ.ID.NO.:15) and amino acid (SEQ.ID.NO.:16) sequences for human GPR35 were thereafter determined and verified.

i. ETBR-LP2 (Seq. Id. Nos. 17 & 18)

ETBR-LP2 was cloned and sequenced in 1998. Valdenaire O. et al., 424(3) *FEBS Lett.* 193 (1998); *see* Figure 1 of Valdenaire for deduced nucleic and amino acid sequences. ETBR-LP2 has an open reading frame of 1839 bp encoding a 613 amino acid protein. ETBR-LP2 has been reported to share homology with the endothelin type B receptor (ETBR-LP). Further, ETBR-LP2 evidences about a 47% amino acid sequence homology with human GPR37. ETBR-LP2 has been reported to be expressed in the human central nervous system (*e.g.*, cerebral cortex, internal capsule fibers and Bergmann glia (424 *FEBS Lett* at 196).

PCR was performed using brain cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 65°C for 1min and 72 °C for 1.5 min. The 5' PCR contained an EcoRI site with the sequence:

5'-CTGGAATTCTCCTGCTCATCCAGCCATGCGG -3' (SEQ.ID.NO.:35)

and the 3' primer contained a BamHI site with the sequence:

5'-CCTGGATCCCCACCCCTACTGGGGCCTCAG -3' (SEQ.ID.NO.:36).

The resulting 1.5 kb PCR fragment was digested with EcoRI and BamHI and cloned into EcoRI-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.:17) and amino acid (SEQ.ID.NO.:18) sequences for human ETBR-LP2 were thereafter determined and verified.

j. GPR26 (Seq. Id. Nos. 97 & 98)

EST clone HIBB055, a 3' 400bp PCR fragment used to screen the Human Genomic lambda Dash II Library (Stratagene catalog special order). The screening conditions were as follows: filters were hybridize overnight at 55°C in a formamide based hybridization

solution. The washing conditions were 2X SSC/1%SDS twice at 65° and .2X SSC/.1%SDS twice at 65°C for 20min at each wash. The filters were placed on film exposed overnight at -80°C and developed the next day. The positive plaques were further characterized by a second round of phage screening from the primary plugs under the same conditions.

Human Fetal Brain cDNA library Uni-ZAP XR Vector (catalog#937227, Stratagene) was then probed with a 250bp probe generated from new sequence from the genomic library screening. The 250bp probe was generated by PCR with *Taqplus Precision* PCR system (Stratagene #600210) with manufacturer supplied buffer system. The cycling parameters were as follows: 30 cycles with 95°C for 45sec, 55°C for 40sec, 72°C for 1min and final extension for 10 min. The primers utilized were as follows:

5'-CGAGAAGGTGCTCAAGGTGGC-3' (SEQ.ID.NO.: 99) and

5'-GAGAAGAGCTCCACTAGCCTGGTGATCACA-3' (SEQ. ID.NO.:100).

The Human Fetal Brain cDNA library was probed with the same 250bp PCR fragment under the same conditions as the genomic library except the hybridization temp was 42°C. The positive primary plugs were further characterized by a second round of screening under the same conditions with a hybridization temp. of 55°C. Positive plaques were analyzed by sequence via Sanger method and the start codon was obtained from one of the positive clones

The human GPR26 full length clone was then generated by PCR using PfuTurbo DNA Polymerase (Stratagene #600250) with the following parameters:

40 cycles of 95°C for 45 sec., 62°C for 1 min. and 72°C for 1.2 min. and a final extension of 10 min. at 72°C. The template used was Human Fetal Brain cDNA (Clonetech# 7402-1) and the primers were as follows:

5'-GAATTCATGAACTCGTGGGACGCGGGCCTGGCGGGC-3' (SEQ.ID.NO.:101)

and

5'-CTCGAGTCACTCAGACACCGGCAGAATGTTCT-3' (SEQ.ID.NO.:102).

The fragment generated had a 5' EcoR1 linker and a 3' Xho1 linker. The PCR product was digested using the given linker enzymes and subcloned into the expression vector pcDNA3.1(+) (Invitrogen#V790-20) at the EcoR1/Xho1 sites using the Rapid Ligation Kit (Roche#1635 379). Nucleic acid (SEQ.ID.NO.:97) and amino acid (SEQ.ID.NO.:98) sequences for human GPR26 were thereafter determined and verified.

Example 2

PREPARATION OF NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED GPCRS

Those skilled in the art are credited with the ability to select techniques for mutation of a nucleic acid sequence. Presented below are approaches utilized to create non-endogenous versions of several of the human GPCRs disclosed above. The mutations disclosed below are based upon an algorithmic approach whereby the 16th amino acid (located in the IC3 region of the GPCR) from a conserved proline (or an endogenous, conservative substitution therefore) residue (located in the TM6 region of the GPCR, near the TM6/IC3 interface) is mutated, preferably to an alanine, histimine, arginine or lysine amino acid residue, most preferably to a lysine amino acid residue.

1. Site-Directed Mutagenesis

Preparation of non-endogenous human GPCRs was accomplished on human GPCRs using, *inter alia*, Transformer Site-Directed™ Mutagenesis Kit (Clontech) according to the manufacturer instructions or QuikChange™ Site-Directed™ Mutagenesis Kit (Stratagene, according to manufacturer's instructions). The following GPCRs were mutated according with the above method using the designated sequence primers (Table C).

For convenience, the codon mutation to be incorporated into the human GPCR is also noted, in standard form (Table C):

TABLE C

Receptor Identifier	Codon Mutation	5'-3' orientation, mutation sequence underlined (SEQ.ID.NO.)	5'-3' orientation (SEQ.ID.NO.)
FLPR-2	T240K	TCCAGCCGTCCCAAACGT GTCTTCGCTGC (37)	CTCCTTCGGTCCTCCTA TCGTTGTCAGAAGT (38)
STRL33	L230K	CAGAAGCACAGATCAAA AAAGATCATCTTCCTG (39)	CTCCTTCGGTCCTCCTA TCGTTGTCAGAAGT (38)
mGluR7	W590S	AGTGGCACTCCCCCTCG GCTGTGATTCCTGT (59)	ACAGGAATCACAGCC GAGGGGGAGTGCCAC T (40)
	R659H	TGTGTTCTTTCCGGCATG TTTTCTTGGGCTTG (41)	CAAGCCCAAGAAAAC ATGCCGGAAAGAACA CA (42)
	T771C	CTCATGGTCACATGTTGT GTGTATGCCATCAAG (43)	CTTGATGGCATACACA CAACATGTGACCATGA G (44)
	I790K	ACGAAGCCAAGCCCAAG GGATTCACTATGTACAC (45)	GTGTACATAGTGAATC CCTTGGGCTTGGCTCC GT (46)
GPR37	L352R	GTCACCACCTTTCACCCG ATGTGCTCTGTGCATAG (47)	CTATGCACAGAGCAC ATCGGGTGAAAGGTG GTGAC (48)
	C543Y	CCTTTTGTTCTTTAAGTC CTATGTCACCCCAGTCCT (49)	AGGACTGGGGTGACA TAGGACTTAAAGAAC AAAAGG (50)
HF1948	I281F	ATGTGGAGCCCCATCTT CATCACCATCCTCC (51)	GGAGGATGGTGATGA AGATGGGGCTCCACAT (52)
	E135N	GCCGCGGTCAGCCTGAA TCGCATGGTGTGCATC (53)	GATGCACACCATGCG ATTCAGGCTGACCGCG GC (54)
GPR66	T273K	GGCCGGAGACAAGTGAA AAGATGCTGTTT (55)	AAACAGCATCTTTTTC ACTTGTCTCCGGCC (56)
GPR35	A216K	*See alternate approaches*	*See alternate approaches*
ETBR-LP2	N358K	GAGAGCCAGCTCAAGAG CACCGTGGTG (57)	CTCCTTCGGTCCTCCTA TCGTTGTCAGAAGT (58)

5

1. **Alternative Approaches For Creation of Non-Endogenous Human GPCRs**

Preparation of the non-endogenous, constitutively activated human GPR35 receptor was accomplished by creating a A216K mutation. Mutagenesis was performed using Transformer Site-Directed™ Mutagenesis Kit (Clontech) according to manufacturer's instructions. (*see*, SEQ.ID.NO.:84 for nucleic acid sequence, SEQ.ID.NO.:85 for amino acid sequence). The two mutagenesis primers were utilized, a lysine mutagenesis oligonucleotide and a selection marker oligonucleotide, which had the following sequences:

5'- GCCACCCGCAAGGCTAAACGCATGGTCTGG -3' (SEQ.ID.NO.:60 sense) and

5'- CTCCTTCGGTCCTCCTATCGTTGTCAGAAGT -3' (SEQ.ID.NO.:61; antisense),

respectively.

For first round PCR, SEQ.ID.NO.:33 and SEQ.ID.NO.:61 were used to generate the 5' 700 bp fragment, while SEQ.ID.NO.:34 and SEQ.ID.NO.:60 were used to generate the 3' 350 bp fragment. PCR was performed using endogenous GPR35 cDNA as template and pfu polymerase (Stratagene) with the buffer system provided by the manufacturer supplemented with 10% DMSO, 0.25 μM of each primer, and 0.5 mM of each 4 nucleotides. The cycle condition was 25 cycles of 94°C for 30 sec, 65°C for 1min and 72 °C for 2 min and 20 sec. The 5' and 3' PCR fragment from first round PCR were then used as cotemplate to perform second round PCR using oligo 1 and 2 as primers and pfu polymerase as described above except the annealing temperature was 55 °C, and the extention time was 2 min. The resulting PCR fragment was then digested and subcloned into pCMV as described for the endogenous cDNA.

The non-endogenous human GPCRs were then sequenced and the derived and verified nucleic acid and amino acid sequences are listed in the accompanying "Sequence Listing" appendix to this patent document, as summarized in Table D below:

TABLE D

Non—Endogenous Receptor	Nucleic Acid Sequence Listing	Amino Acid Sequence Listing
FPRL-2		
L240K	SEQ.ID.NO.:62	SEQ.ID.NO.:63
STRL33		
L230K	SEQ.ID.NO.:64	SEQ.ID.NO.:65
MgluR7		
W590S	SEQ.ID.NO.: 66	SEQ.ID.NO.:67
R659H	SEQ.ID.NO.:68	SEQ.ID.NO.:69
T771C	SEQ.ID.NO.:70	SEQ.ID.NO.:71
I790K	SEQ.ID.NO.:72	SEQ.ID.NO.:73
GPR37		
L352R	SEQ.ID.NO.:74	SEQ.ID.NO.:75
C543Y	SEQ.ID.NO.:76	SEQ.ID.NO.:77
HF1948		
I281F	SEQ.ID.NO.:78	SEQ.ID.NO.:79
E135N	SEQ.ID.NO.:80	SEQ.ID.NO.:81
GPR66		
T273K	SEQ.ID.NO.:82	SEQ.ID.NO.:83
GPR35		
A216K	SEQ.ID.NO.:84	SEQ.ID.NO.:85
ETBR-LP2		
N358K	SEQ.ID.NO.:86	SEQ.ID.NO.:87

Example 3
RECEPTOR EXPRESSION

Although a variety of cells are available to the art-skilled for the expression of proteins, it is preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary pathways that have evolved for mammalian systems – thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as those obtained using mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan.

a. Transient Transfection of 293 Cells

On day one, $6x10^6$ cells/10 cm dish of 293 cells well were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 4μg DNA (*e.g.*, pCMV vector, pCMV vector with receptor cDNA, *etc.*) in 0.5 ml serum free DMEM (Gibco BRL); tube B was prepared by mixing 24μl lipofectamine (Gibco BRL) in 0.5ml serum free DMEM. Tubes A and B were admixed by inversion (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 1XPBS, followed by addition of 5 ml serum free DMEM. One ml of the transfection mixture were added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture was removed by aspiration, followed by the addition of 10ml of DMEM/10% Fetal Bovine Serum. Cells were incubated at 37°C/5% CO_2. After 48hr incubation, cells were harvested and utilized for analysis.

b. Stable 293 Cell Lines

Approximately $12x10^6$ 293 cells will be plated on a 15cm tissue culture plate, and grown in DME High Glucose Medium containing 10% fetal bovine serum and one percent sodium pyruvate, L-glutamine, and antibiotics. Twenty-four hours following plating of 293 cells (to approximately ~80% confluency), the cells will be transfected using 12μg of DNA. The 12μg of DNA is combined with 60μl of lipofectamine and 2mL of DME High Glucose Medium without serum. The medium will be aspirated from the plates and the cells washed once with medium without serum. The DNA, lipofectamine, and medium mixture will be added to the plate along with 10mL of medium without serum. Following incubation at 37°C for four to five hours, the medium will be aspirated and 25ml of medium containing serum will be added. Twenty-four hours following transfection, the medium will be

aspirated again, and fresh medium with serum will be added. Forty-eight hours following transfection, the medium will be aspirated and medium with serum will be added containing geneticin (G418 drug) at a final concentration of 500μg/mL. The transfected cells will then undergo selection for positively transfected cells containing the G418 resistant gene. The medium will be replaced every four to five days as selection occurs. During selection, cells will be grown to create stable pools, or split for stable clonal selection.

c. **RGT CELLS (USED FOR MGLUR7)**

RGT cells were derived from an adenovirus transformed Syrian hamster cell line (AV12-664) into which a glutamate-aspartate transporter was stably transfected.

On day one, $5x10^6$/ 10 cm dish of RGT cells were plated out. On day two, 91μl of serumfree media was added to a tube, followed by the addition of 9μl of Fugene 6 (Roche). To the same mix 3 ug of DNA was added (at 0.5 ug/ul). The mixture was gently mixed and incubated at room temperature for 15 min, then this mixture was added dropwise to the cells growing in DMEM/10% FBS and incubated for 48 hours at 37°C/5% CO_2. After 48hr incubation, cells were harvested and utilized for analysis.

Example 4
ASSAYS FOR DETERMINATION OF CONSTITUTIVE ACTIVITY OF NON-ENDOGENOUS GPCRS

A variety of approaches are available for assessment of constitutive activity of the non-endogenous human GPCRs. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially beneficial for the needs of the artisan.

1. **Membrane Binding Assays: [^{35}S]GTPγS Assay**

When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the

release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. Constitutively activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [^{35}S]GTPγS, can be utilized to demonstrate enhanced binding of [^{35}S]GTPγS to membranes expressing constitutively activated receptors. Advantages of using [^{35}S]GTPγS binding to measure constitutive activation include but are not limited to the following: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

The assay takes advantage of the ability of G protein coupled receptors to stimulate [^{35}S]GTPγS binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to constitutively activated G protein-coupled receptors. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

The [^{35}S]GTPγS assay is incubated in 20 mM HEPES and between 1 and about 20mM $MgCl_2$ (this amount can be adjusted for optimization of results, although 20mM is preferred) pH 7.4, binding buffer with between about 0.3 and about 1.2 nM [^{35}S]GTPγS (this amount can be adjusted for optimization of results, although 1.2 is preferred) and 12.5 to 75 μg membrane protein (*e.g.*, 293 cells expressing the G_s Fusion Protein; this amount can be adjusted for optimization) and 10 μM GDP (this amount can be changed for optimization) for 1 hour. Wheatgerm agglutinin beads (25 μl; Amersham) will then be added and the mixture incubated for another 30 minutes at room temperature. The tubes will be then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter.

2. Cell-based cAMP Detection Assay

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells can contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells were harvested approximately twenty four hours after transient transfection. Media was carefully aspirated and discarded. Ten ml of PBS was gently added to each dish of cells followed by careful aspiration. One ml of Sigma cell dissociation buffer and 3ml of PBS was added to each plate. Cells were pipetted off the plate and the cell suspension collected into a 50ml conical centrifuge tube. Cells were centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet was carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells were then counted using a hemocytometer and additional PBS was added to give the appropriate number of cells (to a final volume of about 50µl/well).

cAMP standards and Detection Buffer (comprising 1 µCi of tracer [^{125}I cAMP (50 µl] to 11 ml Detection Buffer) was prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 50µl of Stimulation Buffer, 3µl of test compound (12µM final assay concentration) and 50µl cells, Assay Buffer was be stored on ice until utilized. The assay was initiated by addition of 50µl of cAMP standards to appropriate wells followed by addition of 50µl of PBSA to wells H-11 and H12. Fifty µl of Stimulation Buffer was added to all wells.

DMSO (or selected candidate compounds) was added to appropriate wells using a pin tool capable of dispensing 3µl of compound solution, with a final assay concentration of 12µM test compound and 100µl total assay volume. The cells were then added to the wells and incubated for 60 min at room temperature. One hundred µl of Detection Mix containing tracer cAMP was then added to the wells. Plates were incubated for an additional 2 hours followed by counting in a Wallac MicroBeta™ scintillation counter. Values of cAMP/well were then extrapolated from a standard cAMP curve which were contained within each assay plate.

3. Co-Transfection of Gi Coupled FPRL-2 with a Gs/Gi Fusion Protein Construct

The transfection mixture (from Example 3A) containing FPRL-2 and Gs/Gi Fusion Protein Construct was removed by aspiration, followed by the addition of 10ml of DMEM/10% Fetal Bovine Serum. Cells were then incubated at 37°C/5% CO_2. After 48hr incubation, cells were harvested and utilized for analysis. Cell-based cAMP detection assay was then performed according to the protocol in Example 4(2) above.

Because endogenous FPRL-2 is believed to predominantly couple with the Gi protein in its active state, a decrease in cAMP production signifies that the disclosed non-endogenous version of FPRL-2 is constitutively active. Thus, a candidate compound which impacts the FPRL-2 receptor by increasing the cAMP signal is an inverse agonist, while a FPRL-2 agonist will decrease the cAMP signal. *See*, Figure 1.

Figure 1 evidence about a 4 fold increase in activity of FPRL-2 when compared to the Gs/Gi. When comparing the endogenous version of FPRL-2 with that of the non-endogenous version, the non-endogenous FPRL-2 ("FPRL-2(L240K)")) evidence about a 3 fold increase in receptor activity when compared to the control, Gs/Gi. Therefore, this data

suggests that both the endogenous and non-endogenous versions of FPRL-2 are constitutively active.

Reference is made to Figure 9. In Figure 9, non-endogenous GPR37(L352R) produced about a 354% increase in cAMP when compared with the endogenous version of GPR37 ("GPR37 wt"), while GPR37(C543Y) produced about a 189% increase in cAMP when compared with GPR37 wt. This data suggests that both non-endogenous L352R and C543Y versions of GPR37 are constitutively activated.

4. Cell-Based cAMP for G_i Coupled Target GPCRs

TSHR is a G_s coupled GPCR that causes the accumulation of cAMP upon activation. TSHR will be constitutively activated by mutating amino acid residue 623 (*i.e.*, changing an alanine residue to an isoleucine residue). A G_i coupled receptor is expected to inhibit adenylyl cyclase, and, therefore, decrease the level of cAMP production, which can make assessment of cAMP levels challenging. An effective technique for measuring the decrease in production of cAMP as an indication of constitutive activation of a G_i coupled receptor can be accomplished by co-transfecting, most preferably, non-endogenous, constitutively activated TSHR (TSHR-A623I) (or an endogenous, constitutively active G_s coupled receptor) as a "signal enhancer" with a G_i linked target GPCR to establish a baseline level of cAMP. Upon creating a non-endogenous version of the G_i coupled receptor, this non-endogenous version of the target GPCR is then co-transfected with the signal enhancer, and it is this material that can be used for screening. This approach will be utilized to effectively generate a signal when a cAMP assay is used; this approach is preferably used in the direct identification of candidate compounds against G_i coupled receptors. It is noted that for a G_i coupled GPCR, when this approach is used, an inverse

agonist of the target GPCR will increase the cAMP signal and an agonist will decrease the cAMP signal.

Cells were transfected according to Example 3A above. The transfected cells were then transfected cells will be harvested approximately twenty four hours after transient transfection. Cell-based cAMP detection assay was then performed according to the protocol in Example 4(2) above.

Preferably, and as noted previously, to ensure that a small molecule candidate compound is targeting the Gi coupled target receptor and not, for example, the TSHR(A623I), the directly identified candidate compound is preferably screened against the signal enhancer in the absence of the target receptor.

Reference is made to Figure 3. Figure 3 is a comparative analysis of endogenous GPR45 ("GPR45 wt") versus a control ("CMV") in 293 cells. Endogenous target receptor GPR45 was co-transfected with a signal enhancer, TSHR(A623I). In the absence of TSH, the endogenous ligand for TSH receptor, co-transfection of TSHR(A623I) with endogenous GPR45 evidence about a 96% decrease in production of cAMP when compared with the control (CMV). In the presence of TSH, endogenous GPR45 ("GPR45 wt") evidence about a 73% decrease in cAMP production when compared to the control ("CMV"). This data indicates that GPR45 is endogenously constitutively active and couples through the Gi protein.

Reference is made to Figure 4 and Table E. Table E is a summary of Figure 4, which is a comparative analysis of endogenous mGluR7 ("mGluR7 wt") with several non-endogenous versions of mGluR7 ("W590S," "R659H," "T771C" and "I790K") and the control ("pCMV") in 293 cells. Table E summarizes the cAMP production of the vector containing the signal enhancer receptor (*i.e.*, TSHR(A623I)) with the target receptor

(mGluR7) in the absence of its endogenous ligand (*i.e.*, TSH); the cAMP production of the co-transfection of the signal enhancer with the target receptor in the presence of TSH percent (%) decrease, in cAMP production, between the endogenous version of mGluR7 and the non-endogenous versions of mGluR7, co-transfected with TSHR(A623I) in the presence of TSH. This data evidences that the non-endogenous versions of mGluR7 ("W590S," "R659H," "T771C" and "I790K") reduce the production of cAMP when compared to the endogenous mGluR7, and thus has been constitutively activated by the methods disclosed above.

TABLE E

Versions of mGluR7	Co-Transfection of 1) Vector-TSHR(A623I) 2) mGluR7 versions 3) without 16mU/ml TSH (pmol cAMP)	Co-Transfection of 1) Vector-TSHR(A623I) 2) mGluR7 versions 3) 16mU/ml TSH (pmol cAMP)	Percent (%) Decrease between Endogenous and Non-endogenous Version of mGluR7 (with TSH)	mGluR7 Inverse Agonist	MGluR7 Agonist
pCMV (without TSHR)	4	–	–		
pCMV	23	288	–		
MgluR7 wt	21	402	0	Increase	Decrease
W590S	9	138	66		
R659H	7	156	61		
T771C	7	156	61		
I790K	9	151	62		

Versions of mGluR7 transfected in RGT cells support the data of above. Reference is made to Figure 5. In Figure 5, W590S evidenced about a 52% decrease in cAMP production; R659H evidenced about a 43% reduction; T771C evidenced about a 5% reduction; and I790K evidenced about a 28% reduction in the production of cAMP when compared to the endogenous version of mGluR7 receptor.

Because mGluR7 predominantly couples with Gi in its active state, a decrease in cAMP production signifies that the disclosed non-endogenous versions of mGluR7 are constitutively active. Thus, a candidate compound which impacts the mGluR7 receptor by increasing the cAMP signal is an inverse agonist, while a mGluR7 agonist will decrease the cAMP signal. Based upon the data generated for Figures 5 and 6, "W590S," "R659H," "T771C" and "I790K"are preferred non-endogenous versions of mGluR7, most preferably is "W590S" when used in a TSHR constitutively activated co-transfection approach using a cAMP assay in both 293 and RGT cells.

Reference is made to Figure 12. In Figure 12, non-endogenous versions of HF1948 ("I281F" and "E135N") evidenced a reduction in cAMP production, about an 18% and about a 39% reduction, respectively, when compared to the endogenous version of HF1948 ('wt'). This data suggests that both non-endogenous I281F and E135N versions of HF1948 are constitutively activated. This decrease in cAMP further suggests that these versions may be Gi-coupled. In addition to being Gi-coupled, Figure 11 suggests that non-endogenous I281F version of HF1948 may also couple to Gq G protein. (*See*, Example 4(5)(f) below).

Reference is made to Figure 16. Figure 16 evidences about a 36% decrease in cAMP production of cells co-transfected with TSHR-A623I ("TSHR-A623I") (in the presence of TSH) and non-endogenous, constitutively activated ETBR-LP2 ("N358K") (65.96 pmole cAMP/well) compared to TSHR-A623I with endogenous ETBR-LP2 ("WT") (102.59 pmol cAMP/well). About a 77% and about a 65% decrease in production of cAMP was evidenced when comparing TSHR-A623I co-transfected with ETBR-LP2("N358K") and TSHR-A623I co-transfected with ETBR-LP2("WT") against TSHR-A623I co-transfected with pCMV (290.75 pmol cAMP/well), respectively. Preferably, this approach

is used for screening an inverse agonist, which would increase the signal, whereas an agonist should decrease the signal. To confirm that a small molecule binds ETBR-LP2 and not to the TSHR-A623I construct, the small molecule is preferably screened against the construct in the absence of ETBR-LP2.

5. Reporter-Based Assays

a. CRE-LUC Reporter Assay (G_s -associated receptors)

293 and 293T cells were plated-out on 96 well plates at a density of 2×10^4 cells per well and were transfected using Lipofectamine Reagent (BRL) the following day according to manufacturer instructions. A DNA/lipid mixture was prepared for each 6-well transfection as follows: 260ng of plasmid DNA in 100µl of DMEM are gently mixed with 2µl of lipid in 100µl of DMEM (the 260ng of plasmid DNA consisted of 200ng of a 8xCRE-Luc reporter plasmid, 50ng of pCMV comprising endogenous receptor or non-endogenous receptor or pCMV alone, and 10ng of a GPRS expression plasmid (GPRS in pcDNA3 (Invitrogen)). The 8XCRE-Luc reporter plasmid is prepared as follows: vector SRIF-β-gal was obtained by cloning the rat somatostatin promoter (-71/+51) at BglV-HindIII site in the pβgal-Basic Vector (Clontech). Eight (8) copies of cAMP response element were obtained by PCR from an adenovirus template AdpCF126CCRE8 (*see*, 7 *Human Gene Therapy* 1883 (1996)) and cloned into the SRIF-β-gal vector at the Kpn-BglV site, resulting in the 8xCRE-β-gal reporter vector. The 8xCRE-Luc reporter plasmid was generated by replacing the beta-galactosidase gene in the 8xCRE-β-gal reporter vector with the luciferase gene obtained from the pGL3-basic vector (Promega) at the HindIII-BamHI site. Following 30 min. incubation at room temperature, the DNA/lipid mixture was diluted with 400 µl of DMEM and 100µl of the diluted mixture was added to each well. One hundred µl of DMEM with 10% FCS was

added to each well after a 4hr incubation in a cell culture incubator. The following day the transfected cells were changed with 200 µl/well of DMEM with 10% FCS. Eight hours later, the wells were changed to 100 µl /well of DMEM without phenol red, after one wash with PBS. Luciferase activity was measured the next day using the LucLite™ reporter gene assay kit (Packard) following manufacturer's instructions and read on a 1450 MicroBeta™ scintillation and luminescence counter (Wallac).

Reference is made to Figure 2. Figure 2 evidences about a 50% decrease in activity of STRL33 when compared to the control (CMV) at 12.5ng of STRL33 receptor. When comparing the endogenous version of STRL33 with that of the non-endogenous version, the non-endogenous STRL33 ("STRL33(L230K)") evidence about a 30% decrease in receptor activity when comparing at 12.5ng of protein, and about a 40% decrease in activity at 25 ng of protein. This data suggests that non-endogenous version of STRL33 receptor is constitutively active and may couple to the G protein, Gi.

b. AP1 reporter assay (G_q-associated receptors)

A method to detect G_q stimulation depends on the known property of G_q-dependent phospholipase C to cause the activation of genes containing AP1 elements in their promoter. A Pathdetect™ AP-1 cis-Reporting System (Stratagene, Catalogue # 219073) was utilized following the protocol set forth above with respect to the CREB reporter assay, except that the components of the calcium phosphate precipitate were 410 ng pAP1-Luc, 80 ng pCMV-receptor expression plasmid, and 20 ng CMV-SEAP.

Reference is made to Figure 17. Figure 17 represents a 61.1% increase in activity of the non-endogenous, constitutively active version of human ETBR-LP2 ("N358K") (2203 relative light units) compared with that of the endogenous ETBR-LP2 (862 relative

light units). This data suggests that non-endogenous version of ETBR-LP2 receptor is constitutively active and may couple to the G protein, Gi.

c. SRF-LUC Reporter Assay (G_q- associated receptors)

One method to detect G_q stimulation depends on the known property of G_q-dependent phospholipase C to cause the activation of genes containing serum response factors in their promoter. A Pathdetect™ SRF-Luc-Reporting System (Stratagene) can be utilized to assay for G_q coupled activity in, *e.g.*, COS7 cells. Cells are transfected with the plasmid components of the system and the indicated expression plasmid encoding endogenous or non-endogenous GPCR using a Mammalian Transfection™ Kit (Stratagene, Catalogue #200285) according to the manufacturer's instructions. Briefly, 410 ng SRF-Luc, 80 ng pCMV-receptor expression plasmid and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) are combined in a calcium phosphate precipitate as per the manufacturer's instructions. Half of the precipitate is equally distributed between 3 wells in a 96-well plate, kept on the cells in a serum free media for 24 hours. The last 5 hours the cells are incubated with 1μM Angiotensin, where indicated. Cells are then lysed and assayed for luciferase activity using a Luclite™ Kit (Packard, Cat. # 6016911) and "Trilux 1450 Microbeta" liquid scintillation and luminescence counter (Wallac) as per the manufacturer's instructions. The data can be analyzed using GraphPad Prism™ 2.0a (GraphPad Software Inc.).

d. SRE Reporter Assay

A SRE-Luc Reporter (a component of Mercury Luciferase System 3, Clontech Catalogue # K2053-1) was utilized in 293 cells. Cells were transfected with the plasmid

components of this system and the indicated expression plasmid encoding endogenous or non-endogenous receptor using Lipofectamine Reagent (Gibco/BRL, Catalogue #18324-012) according to the manufacturer's instructions. Briefly, 420ng SRE-Luc, 50ng CMV (comprising the GPR37 receptor) and 30 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) were combined in a cationic lipid-DNA precipitate as per the manufacturer's instructions. The final volume was 25µl brought up with Optimem (Vendor). This is referred to as the "template mix." The template mix was combined with the lipfectamine in a polystrene tube and was incubated for 30 minutes. During the incubation, the cells were washed with 100µl Optimem. After incubation, 200µl of Optimem was added to mix and 40µl-50µl/well. The cells were left to mix overnight. The media was replaced with fresh medium the following morning to DMEM/Phenol red free/1% FBNS at 130µl/well. The The cells were then assayed for luciferase activity using a Luclite™ Kit (Packard, Cat. # 6016911) and "Trilux 1450 Microbeta" liquid scintillation and luminescence counter (Wallac) as per the manufacturer's instructions. The data were analyzed using GraphPad Prism™ 2.0a (GraphPad Software Inc.).

Reference is made to Figure 7. In Figure 7, when comparing the non-endogenous version of GPR37 ("C543Y") with the endogenous version ("wt"), the C543Y mutation evidences about a 316% increase in cAMP production over the wt version, while the non-endogenous version "L352R" evidence about a 178% increase in production of cAMP over the wt version. This data suggests that both non-endogenous versions of GPR37, C543Y and L352R, are constitutively activated.

e. E2F-Luc Reporter Assay

A pE2F-Luc Reporter (a component of Mercury Luciferase System 3, Clontech Catalogue # K2053-1) was utilized in 293A cells. Cells were transfected with the plasmid components of this system and the indicated expression plasmid encoding endogenous or non-endogenous receptor using Lipofectamine Reagent (Gibco/BRL, Catalogue #18324-012) according to the manufacturer's instructions. Briefly, 400 ng pE2F-Luc, 80 ng CMV (comprising the GPR35 receptor) and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) were combined in a cationic lipid-DNA precipitate as per the manufacturer's instructions. Half of the precipitate was equally distributed over 3 wells in a 96-well plate, kept on the cells overnight, and replaced with fresh medium the following day. Forty-eight (48) hr after the start of the transfection, cells were treated and assayed for luciferase activity using a Luclite™ Kit (Packard, Cat. # 6016911) and "Trilux 1450 Microbeta" liquid scintillation and luminescence counter (Wallac) as per the manufacturer's instructions. The data were analyzed using GraphPad Prism™ 2.0a (GraphPad Software Inc.).

Reference is made to Figure 14. Figure 14 represents about a 100% increase in activity of the non-endogenous, constitutively active version of human GPR35 (A216K) (607.13 relative light units) compared with that of the endogenous GPR35 (24.97 relative light units). This data suggests that GPR35(A216K) interacts with the transcription factor E2F to drive the expression of the luciferase protein. Such interaction with E2F, along with evidence that GPR35 is expressed in colorectal cancer cells, further suggests that GPR35 may play a role in cancer cell proliferation. Thus, based upon these data, a preferred candidate compound which impacts the GPR35 receptor would be an inverse agonist. This

data suggest that an inverse agonist of GPR35 would be useful in the treatment of cancerous conditions, colorectal cancer in particular.

f. Intracellular IP_3 Accumulation Assay (G_q-associated receptors)

On day 1, cells comprising the receptors (endogenous and/or non-endogenous) are plated onto 24 well plates, usually $1x10^5$ cells/well (although his number can be optimized. On day 2 cells were transfected by firstly mixing 0.25ug DNA in 50 µl serum free DMEM/well and 2 µl lipofectamine in 50 µl serum free DMEM/well. The solutions were gently mixed and incubated for 15-30 min at room temperature. Cells were then washed with 0.5 ml PBS and 400 µl of serum free media and then mixed with the transfection media and added to the cells. The cells were incubated for 3-4 hrs at 37°C/5%CO_2 and then the transfection media was removed and replaced with 1ml/well of regular growth media. On day 3 the cells are labeled with ^{3}H-myo-inositol. Briefly, the media was removed and the cells are washed with 0.5 ml PBS. Then 0.5 ml inositol-free/serum free media (GIBCO BRL) were added/well with 0.25 µCi of ^{3}H-myo-inositol/ well and the cells incubated for 16-18 hrs overnight at 37°C/5%CO_2. On Day 4 the cells are washed with 0.5 ml PBS and 0.45 ml of assay medium was added containing inositol-free/serum free media 10 µM pargyline 10 mM lithium chloride or 0.4 ml of assay medium. The cells were then incubated for 30 min at 37°C. The cells are then washed with 0.5 ml PBS and 200 µl of fresh/ice cold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) is added to each well. The solution was kept on ice for 5-10 min (or until cells are lysed) and then neutralized by 200 µl of fresh/ice cold neutralization solution (7.5 % HCL). The lysate was then transferred into 1.5 ml Eppendorf tubes and 1 ml of chloroform/methanol (1:2) was added/tube. The solution was vortexed for 15 sec and the upper phase was applied to a Biorad AG1-X8™ anion exchange resin (100-200 mesh). First, the resin was washed with

water at 1:1.25 W/V and 0.9 ml of upper phase was loaded onto the column. The column was then washed with 10 ml of 5 mM myo-inositol and 10 ml of 5 mM Na-borate/60mM Na-formate. The inositol tris phosphates were eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns were regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with dd H_2O and stored at 4°C in water.

Reference is made to Figure 6. In Figure 6, 293 cells were transfected with Gq protein containing a six amino acid deletion, "Gq(del)"; Gq protein fused to a Gi protein, "Gq(del)/Gi", and non-endogenous mGluR7, T771C together with Gq(del), "T771C+Gq(del)" and T771C with Gq(del)/Gi, "T771C+Gq(del)/Gi". Inositol triphosphate was measured in the presence and absence of glutamate. Co-transfection of non-endogenous version of mGluR7 with Gq(del)/Gi evidence about a 1850 fold increase when compared to the Gq(del)/Gi in the presence of glutamate; and about a 860 fold increase compared with T771C+Gq(del)/Gi in the presence of glutamate. These data evidences that mGluR7, a Gi coupled receptor, can be activated via the Gq protein. Therefore, the Gq(del)/Gi Fusion Construct can be co-transfected with a GPCR and used to as a tool to screen for candidate compounds.

Reference is made to Figure 11. In Figure 11, when comparing the non-endogenous version of HF1948 ("I281F") with the endogenous version ("wt"), the I281F mutation evidences about a 361% increase in IP3 accumulation over the wt version. This data suggests that the non-endogenous I281F version of HF1948 is constitutively activated and is Gq-coupled.

Example 5
FUSION PROTEIN PREPARATION

a. GPCR: G_s Fusion Construct

The design of the constitutively activated GPCR-G protein fusion construct can be accomplished as follows: both the 5' and 3' ends of the rat G protein $G_s\alpha$ (long form; Itoh, H. et al., 83 *PNAS* 3776 (1986)) is engineered to include a HindIII (5'-AAGCTT-3') sequence thereon. Following confirmation of the correct sequence (including the flanking HindIII sequences), the entire sequence is shuttled into pcDNA3.1(-) (Invitrogen, cat. no. V795-20) by subcloning using the HindIII restriction site of that vector. The correct orientation for the $G_s\alpha$ sequence will be determined after subcloning into pcDNA3.1(-). The modified pcDNA3.1(-) containing the rat $G_s\alpha$ gene at HindIII sequence is then verified; this vector will then be available as a "universal" $G_s\alpha$ protein vector. The pcDNA3.1(-) vector contains a variety of well-known restriction sites upstream of the HindIII site, thus beneficially providing the ability to insert, upstream of the G_s protein, the coding sequence of an endogenous, constitutively active GPCR. This same approach can be utilized to create other "universal" G protein vectors, and, of course, other commercially available or proprietary vectors known to the artisan can be utilized. In some embodiments, the important criteria is that the sequence for the GPCR be upstream and in-frame with that of the G protein.

Spacers in the restriction sites between the G protein and the GPCR are optional. The sense and anti-sense primers included the restriction sites for XbaI and EcoRV, respectively, such that spacers (attributed to the restriction sites) exist between the G protein and the GPCR.

PCR will then be utilized to secure the respective receptor sequences for fusion within the $G_s\alpha$ universal vector disclosed above, using the following protocol for each: 100ng cDNA for GPCR will be added to separate tubes containing 2μl of each primer

(sense and anti-sense), 3µl of 10mM dNTPs, 10µl of 10XTaqPlus™ Precision buffer, 1µl of TaqPlus™ Precision polymerase (Stratagene: #600211), and 80µl of water. Reaction temperatures and cycle times for the GPCR will be as follows with cycle steps 2 through 4 were repeated 35 times: 94°C for 1 min; 94°C for 30 seconds; 62°C for 20 sec; 72°C 1 min 40sec; and 72°C 5 min. PCR products will be run on a 1% agarose gel and then purified. The purified products will be digested with XbaI and EcoRV and the desired inserts purified and ligated into the G_s universal vector at the respective restriction sites. The positive clones will be isolated following transformation and determined by restriction enzyme digestion; expression using 293 cells will be accomplished following the protocol set forth *infra*. Each positive clone for GPCR- G_s Fusion Protein will be sequenced to verify correctness.

g. G_q(6 amino acid deletion)/G_i Fusion Construct

The design of a G_q (del)/G_i fusion construct was accomplished as follows: the N-terminal six (6) amino acids (amino acids 2 through 7), having the sequence of TLESIM (SEQ.ID.NO.:88) Gαq-subunit was deleted and the C-terminal five (5) amino acids, having the sequence EYNLV (SEQ.ID.NO.:89) was replaced with the corresponding amino acids of the Gαi Protein, having the sequence DCGLF (SEQ.ID.NO.:90). This fusion construct was obtained by PCR using the following primers:

5'-gatcAAGCTTCCATGGCGTGCTGCCTGAGCGAGG-3' (SEQ.ID.NO.:91) and

5'-gatcGGATCCTTAGAACAGGCCGCAGTCCTTCAGGTTCAGCTGCAGGATGGTG-3' (SEQ.ID.NO.:92) and Plasmid 63313 which contains the mouse Gαq-wild type version with a hemagglutinin tag as template. Nucleotides in lower caps are included as spacers.

TaqPlus® Precision DNA polymerase (Stratagene) was utilized for the amplification by the following cycles, with steps 2 through 4 repeated 35 times: 95°C for

2 min; 95°C for 20 sec; 56°C for 20 sec; 72°C for 2 min; and 72°C for 7 min. The PCR product will be cloned into a pCRII-TOPO vector (Invitrogen) and sequenced using the ABI Big Dye Terminator kit (P.E. Biosystems). Inserts from a TOPO clone containing the sequence of the fusion construct will be shuttled into the expression vector pcDNA3.1(+) at the HindIII/BamHI site by a 2 step cloning process.

c. Gs/Gi Fusion Protein Construct

The design of a Gs/Gi Fusion Protein Construct was accomplished as follows: the C-terminal five (5) amino acids of Gαs-subunit was deleted, having the sequence 5'-QYELL-3' (SEQ.ID.NO.:93) and replaced with the corresponding amino acids of the Gαi protein, having the sequence 5'-DCGLF-3' (SEQ.ID.NO.:94). This protein fusion construct was obtained by PCR using a 5' and 3' oligonucleotides.

TaqPlus Precision DNA polymerase (Stratagene) was utilized for the amplification by the following cycles, with steps 2 through 4 repeated 25 times: 98°C for 2 min; 98°C for 30 sec; 60°C for 30 sec; 72°C for 2 min; and 72°C for 5 min. The PCR product was cloned into a pCRII-TOPO vector (Invitrogen) and sequenced using the ABI Big Dye Terminator kit (P.E. Biosystems). Inserts from a TOPO clone containing the sequence of the protein fusion construct was shuttled into the expression vector pcDNA3.1(+) at the restriction site. The nuclei acid sequence for Gs/Gi Protein Fusion Construct was then determined. See SEQ.ID.NO.:95 for the nucleic acid sequence and SEQ.ID.NO.:96 for the amino acid sequence.

Example 6
SCHWANN CELL PREPARATION

2L of neonate rat pups (Sprague Dawley) (at Post-pardum day 2-Post-pardum day 3 stage) were placed on ice to euthanize. Pups were then removed and decapitated to drain

the blood. The neonates were placed, belly-down, on a dissection board and rinsed with 70% ethanol to sterilize. Using a scalpel, the skin was removed in the thigh area until the sciatic nerve was exposed (or until a thin white "string" extended from the spinal cord to the knee was visible). The nerves were placed in DMEM medium and then aspirated, followed by bringing the volume to 2.4 ml with DMEM media and adding 300uL 10X Collagenase (0.3%, Sigma Cat. #C-9891) and 300uL 10X Trypsin (0.25%, GIBCO Cat. #25095-019) for dissociation. Nerves were then incubated at 37°C for 15 min, centrifuged for 5 min at 1,000 rpm followed by removing the media (repeated twice). 1 mL DMEM-HEPES and 1mL DMEM/10% FBS were added and then transfered to a 50mL conical tube. The contents of the tube were sheared with the following gauge needles (VWR): once with 18G, twice with 21G and twice with 23G. The contents were placed on a Falcon cell strainer and spun at a very low speed (about 1200 rpm). The total volume was brought to 10mL with DMEM/10% FBS and plated on a Poly-L-lysine treated 10cm plate (Sigma, Cat. #P-1274). Plates were then incubated overnight in 37°C humid incubator at 7% CO2. Fresh media added with 100X ARA C (10mM, Sigma, Cat. #C-1768) and cultured for an additional 48 hours. The cells were then washed with PBS (three times) to remove the ARA C and the following were added: DMEM/10% FBS, different concentrations of Forskolin in 100% ethanol (2uM, 5uM, 10uM, 20uM and 50uM) (Calbiochem, Cat#344270), 80ug of Pituitary Extract (Sigma, #P-1167) in PBS and 0.1%BSA, followed by growing the cells for 30 hours at 37°C humidifier at 7% CO_2. The cells were then collected and the RNA was isolated and analyzed.

Antibody selection was accomplished according to the following: the Poly-L-Lysine treated plates were first washed with 1X PBS (three times), trypsinized with 1mL of 0.5% trypsin-EDTA, for about 1 min and then neutralized with 9mL of DMEM-HEPES buffer

and 10% FBS. Cells were centrifuged at 1200rpm for 5 min, resuspended in 3mL of DMEM-HEPES to wash out the trypsin and spun for 5 min at 1200rpm. Cells were then resuspended in 600uL of DMEM-HEPES, leaving some media after the spin in order to have single cells. Thy1.1 antibody (Monoclonal Antibody, Sigma, Cat. #P-1274) was added at a 1:1000 dilution.

The cells were then incubated for 20 min at 37°C, slightly agitating the tube every two minutes. 20uL of Guinea Pig complement (GIBCO, Cat. #19195-015) was thawed before using it, followed by adding the complement to the cells with the antibody to a final volume of 1mL. The cells were incubated for about 20 min-30 min at 37°C water bath and 10mL of DMEM-HEPES was added and spun down for 5 min at 1200rpm. Cells were resuspended in 5mLs of DMEM/10% FBS and added to poly-L-lysine treated plates that contains pituitary extract and forskolin. The cells were left to recover for 24-48 hours and the immune selection procedure was repeated twice.

EXAMPLE 7

PREPARATION OF CRUSHED RAT SCIATIC NERVE

The sciatic nerves of anesthetized (iso-florene), adult (10-13 week old) Sprague-Dawley rats were exposed at the sciatic notch. Nerve crush was produced by tightly compressing the sciatic nerve at the sciatic notch with flattened forceps twice, each time for 10 sec; this technique causes the axons to degenerate, but allows axonal regeneration. At varying times after nerve injury, the animals were euthanized by CO_2 inhalation, the distal nerve stumps were removed, and the most proximal 2-3 mm was trimmed off. For crushed nerves, the entire distal nerve was harvested. The nerves were immediately frozen in liquid nitrogen and stored at –80°C. Unlesioned sciatic nerves were obtained from animals of varying ages, from P0 (post crush) to P13.

Example 8
TISSUE DISTRIBUTION OF THE DISCLOSED HUMAN GPCRS:

1. RT-PCR

RT-PCR can be applied to confirm the expression and to determine the tissue distribution of several novel human GPCRs. Oligonucleotides utilized will be GPCR-specific and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) will be utilized for the amplification in a 40µl reaction according to the manufacturer's instructions. Twenty µl of the reaction will be loaded on a 1.5% agarose gel to analyze the RT-PCR products.

2. Dot-Blot

Using a commercially available human-tissue dot-blot format, endogenous GPCR was used to probe for a determination of the areas where such receptor is localized. The PCR fragments of Example 1 were used as the probe: radiolabeled probe was generated using this fragment and a Prime-It II™ Random Primer Labeling Kit (Stratagene, #300385), according to manufacturer's instructions. A human RNA Master Blot™ (Clontech, #7770-1) was hybridized with GPCR radiolabeled probe and washed under stringent conditions according manufacturer's instructions. The blot was exposed to Kodak BioMax Autoradiography film overnight at -80°C. Table F, below, lists the receptors and the tissues wherein expression was found. Exemplary diseases/disorders linked to the receptors are discussed in Example 6, *infra*.

TABLE F

Receptor Identifier	Tissue Expression
STRL33	Placenta, spleen and lung
GPR45	Central nervous system, brain
GPR37	central nervous system, specifically in the brain tissues, pituitary gland and placenta

GPR66	pancreas, bone, testis, mammary glands, small intestine, and spleen
GPR26	Brain
ETBR-LP2	Brain, pituitary gland and placenta

3. Northern Blot

a. GPR37

RNA from Example 6 was harvested utilizing RNAzol B reagent (TelTest Inc., Cat. #CS-104), according to manufacturer's instructions. After electrophoresis in an 1% agarose/formaldehyde gel, the RNA was transferred to a nylon membrane (Sachleicher Schull) by capillary action using 10X SSC. A ^{32}P-labelled GPR37 DNA probe was synthesized using a DNA fragment corresponding precisely to the 3' end of GPR37 and a High Prime labeling kit (Roche Molecular Biochemical) according to the manufacturer's instructions. Hybridization was performed using ExpressHyb Solution (Clontech, Cat. #8015-2) supplemented with 100 μg/ml salmon sperm DNA as follows. The membrane containing the separated RNA samples was first incubated with ExpressHyb solution at 65°C overnight. The ^{32}P-labelled GPR37 DNA probe was denatured by boiling for 2 minutes, placed on ice for 5 minutes and then transferred into the ExpressHyb solution bathing the membrane. After an overnight incubation at 65°C, the membrane was removed from the hybridization solution and washed four times for 15 minutes each in 2XSSC/1% SDS at 65°C, followed by two washes for 15 minutes each in 0.2XSSC/0.1% SDS at 55°C. Excess moisture was removed from the blot by gentle shaking, after which the blot was wrapped in plastic wrap and exposed to film overnight at –80°C.

Reference is made to Figure 9. Figure 9 evidences that GPR37 is expressed in Schwann cells, such that myelination can be maintained at 20uM Forskolin.

Figure 10 evidences that GPR37 is up-regulated in crushed rat sciatic nerves, specifically seven (7) days after crushing the nerves. Such data is consistent with the data presented in Figure 9, *i.e.,* GPR37 may play a role in the regeneration of nerves by stimulating the process of myelination in Schwann cells.

GPR37 is expressed in the human central nervous system, specifically in the brain tissues. It has been further determined that GPR37 is expressed in Schwann cells. When axons (or nerves) are injured, Schwann cells act to regenerate the nerves by forming myelin sheaths around the axons, which provides "insulation" in the form of myelin sheaths. This process, known as myelination, is important in that action potentials travel at a faster rate, thereby conserving metabolic energy. Schwann cells and their precursors play an important role in influencing the survival and differentiation of other cells that make up a pheripheral nerve. In addition, GPR37 has been determined to be expressed in crushed rat sciatic nerves. Such data supports the evidence that GPR37 may play a role in regenerating nerve cells. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced. Thus, in the case of hyper-myelination (*e.g.*, tumorgenesis), an inverse agonist against GPR37 is preferred, while an agonist is preferred where hypo-myelination occurs (*e.g.,* a degenerative disease such as diabetes).

b. GPR66

Total RNA from several pancreatic cell lines (*e.g.,* HIT, ARIP, Tu6, RIN αTC, STC, NIT, and EcR-CHO, all of which are commercially available) were isolated using TRIzol reagent (Gibco/BRL, Cat #15596-018) according to manufacturer's instructions. After electrophoreseis in a 1% agarose/formaldehyde gel, the RNA was transferred to a nylon membrane using standard protocols. A ^{32}P-labelled GPR66 probe was synthesized

using a DNA fragment corresponding precisely to the entire coding sequence and a Prime It II Random Primer Labeling Kit (Stratagene, Cat. #300385) according to manufacturer's instructions. Hybridization was performed using ExpressHyb Solution (Clontech, Cat.#8015-2) supplemented with 100ug/ml salmon sperm DNA as follows. The membrane containing the separated RNA samples were first incubated with ExpressHyb solution at 65°C for 1 hour. The ^{32}P-labeled GPR66 DNA probe was denatured by boiling for 2 min, placed on ice for 5 min and then transferred into the ExpressHyb solution bathing the membrane. After an overnight incubation at 65°C, the membrane was removed from the hybridization and washed four times for 15 min each in 2XSSC/1% SDS at 65°C, followed by two washes for 15 min each in 0.1XSSC/0.5% SDS at 55°C. Excess moisture was removed from the blot by gentle shaking, after which the blot was wrapped in plastic and exposed to film overnight at -80°C.

Reference is made to Figure 13. Results of RNA blots (*see*, Figure 13) together with the dot-blot data, evidencing the expression of GPR66 in the pancreas, suggest that GPR66 is abundantly expressed in all islet cell lines and in ARIP cells, a pancreatic ductal cell lines. While not wishing to be bound by any theory, the expression of GPR66 in the pancreatic cell lines suggest that GPR66 may play a role in islet neogenesis.

c. GPR35

Total RNA from several cancer cell lines (*e.g.*, RIN-5AH, HEP-G2, A549, HELA, MOLT-4, HL-60 and SW480 cells, all of which are commercially available) were isolated using TRIzol reagent (Gibco/BRL, Cat #15596-018) according to manufacturer's instructions. After electrophoreseis in a 1% agarose/formaldehyde gel, the RNA was transferred to a nylon membrane using standard protocols. A ^{32}P-labelled GPR35 probe was synthesized using a DNA fragment corresponding precisely to the

entire coding sequence and a Prime It II Random Primer Labeling Kit (Stratagene, Cat. #300385) according to manufacturer's instructions. Hybridization was performed using ExpressHyb Solution (Clontech, Cat.#8015-2) supplemented with 100ug/ml salmon sperm DNA as follows. The membrane containing the separated RNA samples were first incubated with ExpressHyb solution at 65°C for 1 hour. The ^{32}P-labeled GPR35 DNA probe was denatured by boiling for 2 min, placed on ice for 5 min and then transferred into the ExpressHyb solution bathing the membrane. After an overnight incubation at 65°C, the membrane was removed from the hybridization and washed four times for 15 min each in 2XSSC/1% SDS at 65°C, followed by two washes for 15 min each in 0.1XSSC/0.5% SDS at 55°C. Excess moisture was removed from the blot by gentle shaking, after which the blot was wrapped in plastic and exposed to film overnight at

-80°C.

Reference is made to Figure 15. Results of RNA blots (*see,* Figure 15) evidences that GPR35 is abundantly expressed in colorectal cancer cell line SW480. Such data suggests that GPR35 may play a role in colorectal carcinogenesis. Identification of candidate compounds, by the method discussed below, is most preferably an inverse agonist. An inverse agonist for GPR35 is intended to reduce DNA replication in an effort to inhibit cell proliferation of cancerous cells. GPR35 is expressed in large and small intestine. Numerous cancer cell lines were examined where GPR35 was determined to be expressed in the colorectal cancer cell line (e.g., HELA, MOLT-4 and SW480). This data suggests that GPR35 may play a role in colorectal carcinogenesis. Colorectal cancer is a malignancy that arises from either the colon or the rectum. Cancers of the large intestine are the second most common form of cancer found in both males and females.

d. ETBR-LP2

RNA from Example 6 was harvested utilizing RNAzol B reagent (TelTest Inc., Cat. #CS-104), according to manufacturer's instructions. After electrophoresis in an 1% agarose/formaldehyde gel, the RNA was transferred to a nylon membrane (Sachleicher Schull) by capillary action using 10X SSC. A ^{32}P-labelled ETBR-LP2 DNA probe was synthesized using a DNA fragment corresponding precisely to the 3' end of ETBR-LP2 and a High Prime labeling kit (Roche Molecular Biochemical) according to the manufacturer's instructions. Hybridization was performed using ExpressHyb Solution (Clontech, Cat. #8015-2) supplemented with 100 μg/ml salmon sperm DNA as follows. The membrane containing the separated RNA samples was first incubated with ExpressHyb solution at 65°C overnight. The ^{32}P-labelled ETBR-LP2 DNA probe was denatured by boiling for 2 minutes, placed on ice for 5 minutes and then transferred into the ExpressHyb solution bathing the membrane. After an overnight incubation at 65°C, the membrane was removed from the hybridization solution and washed four times for 15 minutes each in 2XSSC/1% SDS at 65°C, followed by two washes for 15 minutes each in 0.2XSSC/0.1% SDS at 55°C. Excess moisture was removed from the blot by gentle shaking, after which the blot was wrapped in plastic wrap and exposed to film overnight at –80°C.

Reference is made to Figure 18. Figure 18 evidences that ETBR-LP2 is expressed in Schwann cells, such that myelination can be maintained at 20uM Forskolin.

Reference is made to Figure 19. Figure 19 evidences that ETBR-LP2 is up-regulated in crushed rat sciatic nerves, specifically seven (7) days after crushing the nerves. Such data is consistent with the data presented in Figure 18, *i.e.,* ETBR-LP2 may play a role in the regeneration of nerves by stimulating the process of myelination in Schwann cells.

Based upon these data, ETBR-LP2 is expressed in Schwann cells. When axons (or nerves) are injured, Schwann cells act to regenerate the nerves by forming myelin sheaths around the axons, which provides "insulation" in the form of myelin sheaths. This process, known as myelination, is important in that action potentials travel at a faster rate, thereby conserving metabolic energy. Schwann cells and their precursors play an important role in influencing the survival and differentiation of other cells that make up a pheripheral nerve. In addition, ETBR-LP2 has been determined to be expressed in crushed rat sciatic nerves. Such data supports the evidence that ETBR-LP2 may play a role in regenerating nerve cells. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced. Thus, in the case of hyper-myelination (*e.g.*, tumorgenesis), an inverse agonist against ETBR-LP2 is preferred, while an agonist is preferred where hypo-myelination occurs (*e.g.*, a degenerative disease such as diabetes).

Diseases and disorders related to receptors located in these tissues or regions include, but are not limited to, cardiac disorders and diseases (*e.g.* thrombosis, myocardial infarction; atherosclerosis; cardiomyopathies); kidney disease/disorders (e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic diabetes insipidus; cystinuria; polycystic kidney disease); eosinophilia; leukocytosis; leukopenia; ovarian cancer; sexual dysfunction; polycystic ovarian syndrome; pancreatitis and pancreatic cancer; irritable bowel syndrome; colon cancer; Crohn's disease; ulcerative colitis; diverticulitis; Chronic Obstructive Pulmonary Disease (COPD); Cystic Fibrosis; pneumonia; pulmonary hypertension; tuberculosis and lung cancer; Parkinson's disease; movement disorders and ataxias; learning and memory disorders; eating disorders (e.g., anorexia; bulimia, etc.); obesity; cancers; thymoma; myasthenia gravis; circulatory disorders; prostate cancer;

prostatitis; kidney disease/disorders(e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic diabetes insipidus; cystinuria; polycystic kidney disease); sensorimotor processing and arousal disorders; obsessive-compulsive disorders; testicular cancer; priapism; prostatitis; hernia; endocrine disorders; sexual dysfunction; allergies; depression; psychotic disorders; migraine; reflux; schizophrenia; ulcers; bronchospasm; epilepsy; prostatic hypertrophy; anxiety; rhinitis; angina; and glaucoma. Accordingly, the methods of the present invention may also be useful in the diagnosis and/or treatment of these and other diseases and disorders.

Example 7
Protocol: Direct Identification of Inverse Agonists and Agonists

A. [^{35}S]GTPγS Assay

Although endogenous, constitutively active GPCRs have been used for the direct identification of candidate compounds as, *e.g.*, inverse agonists, for reasons that are not altogether understood, intra-assay variation can become exacerbated. In some embodiments a GPCR Fusion Protein, as disclosed above, is also utilized with a non-endogenous, constitutively activated GPCR. When such a protein is used, intra-assay variation appears to be substantially stabilized, whereby an effective signal-to-noise ratio is obtained. This has the beneficial result of allowing for a more robust identification of candidate compounds. Thus, in some embodiments it is preferred that for direct identification, a GPCR Fusion Protein be used and that when utilized, the following assay protocols be utilized.

1. Membrane Preparation

Membranes comprising the constitutively active orphan GPCR Fusion Protein of interest and for use in the direct identification of candidate compounds as inverse agonists or agonists are preferably prepared as follows:

a. Materials

"Membrane Scrape Buffer" is comprised of 20mM HEPES and 10mM EDTA, pH 7.4; "Membrane Wash Buffer" is comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4; "Binding Buffer" is comprised of 20mM HEPES, 100 mM NaCl, and 10 mM $MgCl_2$, pH 7.4

b. Procedure

All materials will be kept on ice throughout the procedure. Firstly, the media will be aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold PBS, followed by aspiration. Thereafter, 5ml of Membrane Scrape Buffer will be added to scrape cells; this will be followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm for 17 minutes at 4°C). Thereafter, the supernatant will be aspirated and the pellet will be resuspended in 30ml Membrane Wash Buffer followed by centrifugation at 20,000 rpm for 17 minutes at 4°C. The supernatant will then be aspirated and the pellet resuspended in Binding Buffer. The resuspended pellet will then be homogenized using a Brinkman Polytron™ homogenizer (15-20 second bursts until the material is in suspension). This is referred to herein as "Membrane Protein".

2. Bradford Protein Assay

Following the homogenization, protein concentration of the membranes will be determined, for example, using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and frozen (-80°C) for later use; when frozen, protocol for use will be as follows: on the day of the assay, frozen Membrane Protein is thawed at room

temperature, followed by vortex and then homogenized with a Polytron at about 12 x 1,000 rpm for about 5-10 seconds; it was noted that for multiple preparations, the homogenizer is thoroughly cleaned between homogenization of different preparations).

a. Materials

Binding Buffer (as discussed above); Bradford Dye Reagent; Bradford Protein Standard will be utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

b. Procedure

Duplicate tubes will be prepared, one including the membrane, and one as a control "blank". Each contains 800µl Binding Buffer. Thereafter, 10µl of Bradford Protein Standard (1mg/ml) will be added to each tube, and 10µl of membrane Protein will then be added to just one tube (not the blank). Thereafter, 200µl of Bradford Dye Reagent will be added to each tube, followed by vortexing. After five minutes, the tubes will be re-vortexed and the material therein will be transferred to cuvettes. The cuvettes will then be read using a CECIL 3041 spectrophotometer, at wavelength 595.

3. Direct Identification Assay

a. Materials

GDP Buffer consisted of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 µM GDP (final concentration of GDP in each well was 0.1 µM GDP); each well comprising a candidate compound, has a final volume of 200µl consisting of 100µl GDP Buffer (final concentration, 0.1µM GDP), 50µl Membrane Protein in Binding Buffer, and 50µl [^{35}S]GTPγS (0.6 nM) in Binding Buffer (2.5 µl [^{35}S]GTPγS per 10ml Binding Buffer).

b. Procedure

Candidate compounds will be preferably screened using a 96-well plate format (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the GPCR Fusion Protein, as control), will be homogenized briefly until in suspension. Protein concentration will then be determined using, for example, the Bradford Protein Assay set forth above. Membrane Protein (and controls) will then be diluted to 0.25mg/ml in Binding Buffer (final assay concentration, 12.5µg/well). Thereafter, 100 µl GDP Buffer is added to each well of a Wallac Scintistrip™ (Wallac). A 5µl pin-tool will then be used to transfer 5 µl of a candidate compound into such well (*i.e.*, 5µl in total assay volume of 200 µl is a 1:40 ratio such that the final screening concentration of the candidate compound is 10µM). Again, to avoid contamination, after each transfer step the pin tool is rinsed in three reservoirs comprising water (1X), ethanol (1X) and water (2X) – excess liquid is shaken from the tool after each rinse and the tool is dried with paper and Kim wipes. Thereafter, 50 µl of Membrane Protein will be added to each well (a control well comprising membranes without the GPCR Fusion Protein was also utilized), and pre-incubated for 5-10 minutes at room temperature. Thereafter, 50 µl of [^{35}S]GTPγS (0.6 nM) in Binding Buffer will be added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay will be stopped by spinning the plates at 4000 RPM for 15 minutes at 22°C. The plates will then be aspirated with an 8 channel manifold and sealed with plate covers. The plates will then be read on a Wallac 1450 using setting "Prot. #37" (as per manufacturer's instructions).

B. Cyclic AMP Assay

Another assay approach to directly identify candidate compound will be accomplished utilizing a cyclase-based assay. In addition to direct identification, this assay

approach can be utilized as an independent approach to provide confirmation of the results from the [^{35}S]GTPγS approach as set forth above.

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) will be preferably utilized for direct identification of candidate compounds as inverse agonists and agonists to GPCRs in accordance with the following protocol.

Transfected cells will be harvested approximately three days after transfection. Membranes will be prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$. Homogenization will be performed on ice using a Brinkman Polytron™ for approximately 10 seconds. The resulting homogenate will be centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet will then be resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet will then be stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet will slowly be thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$, to yield a final protein concentration of 0.60mg/ml (the resuspended membranes will be placed on ice until use).

cAMP standards and Detection Buffer (comprising 2 μCi of tracer [^{125}I cAMP (100 μl] to 11 ml Detection Buffer) will be prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer will be prepared fresh for screening and contain 20mM HEPES, pH 7.4, 10mM $MgCl_2$, 20mM phosphocreatine (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 μM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer will be stored on ice until utilized.

Candidate compounds identified as per above (if frozen, thawed at room temperature) will be added, preferably, to 96-well plate wells (3μl/well; 12μM final assay

concentration), together with 40 µl Membrane Protein (30µg/well) and 50µl of Assay Buffer. This admixture will be incubated for 30 minutes at room temperature, with gentle shaking.

Following the incubation, 100µl of Detection Buffer will be added to each well, followed by incubation for 2-24 hours. Plates will then be counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

C. Melanophore Screening Assay

A method for identifying candidate agonists or inverse agonists for a GPCR can be preformed by introducing tests cells of a pigment cell line capable of dispersing or aggregating their pigment in response to a specific stimulus and expressing an exogenous clone coding for the GCPR. A stimulant, *e.g.*, light, sets an initial state of pigment disposition wherein the pigment is aggregated within the test cells if activation of the GPCR induces pigment dispersion. However, stimulating the cell with a stimulant to set an initial state of pigment disposition wherein the pigment is dispersed if activation of the GPCR induces pigment aggregation. The tests cells are then contacted with chemical compounds, and it is determined whether the pigment disposition in the cells changed from the initial state of pigment disposition. Dispersion of pigments cells due to the candidate compound coupling to the GPCR will appear dark on a petri dish, while aggregation of pigments cells will appear light.

Materials and methods will be followed according to the disclosure of U.S. Patent Number 5,462,856 and U.S. Patent Number 6,051,386, each of which are incorporated by reference in its entirety.

Although a variety of expression vectors are available to those in the art, for purposes of utilization for both the endogenous and non-endogenous human GPCRs, in

some embodiments it is preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

References cited throughout this patent document, including co-pending and related patent applications, unless otherwise indicated, are fully incorporated herein by reference. Modifications and extension of the disclosed inventions that are within the purview of the skilled artisan are encompassed within the above disclosure and the claims that follow.

CLAIMS

What is claimed is:

1. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:2.
2. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 1.
3. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:1.
4. A host cell comprising the plasmid of claim 3.
5. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:4.
6. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 5.
7. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:3.
8. A host cell comprising the plasmid of claim 7.
9. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:6.
10. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 9.
11. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:5.
12. A host cell comprising the plasmid of claim 11.
13. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:8.

14. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 13.

15. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:7.

16. A host cell comprising the plasmid of claim 15.

17. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:10.

18. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 17 .

19. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:9.

20. A host cell comprising the plasmid of claim 19.

21. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:12.

22. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 21.

23. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:11.

24. A host cell comprising the plasmid of claim 23.

25. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:14.

26. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 25.

27. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:13.

28. A host cell comprising the plasmid of claim 27.

29. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:16.

30. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 29.

31. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:15.

32. A host cell comprising the plasmid of claim 31.

33. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:18.

34. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 33.

35. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:17.

36. A host cell comprising the plasmid of claim 35.

Figure 1

Cell-Based cAMP Assay

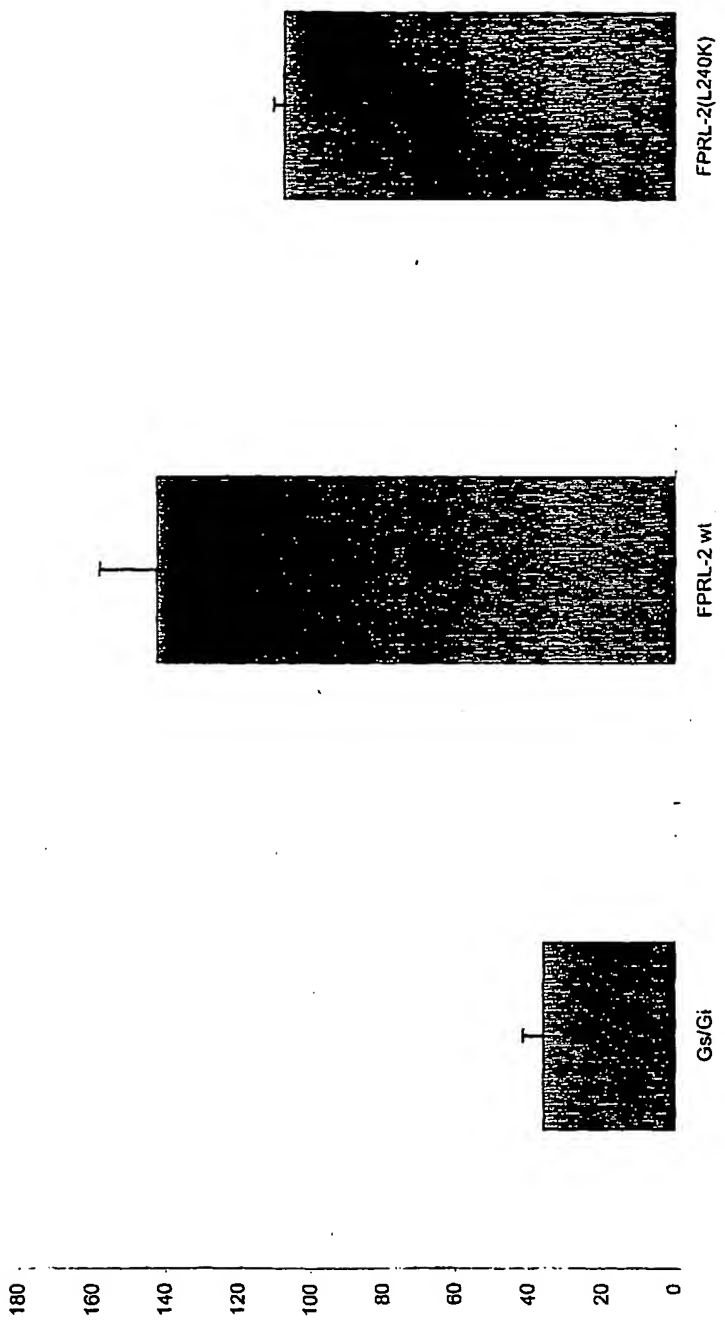


Figure 2

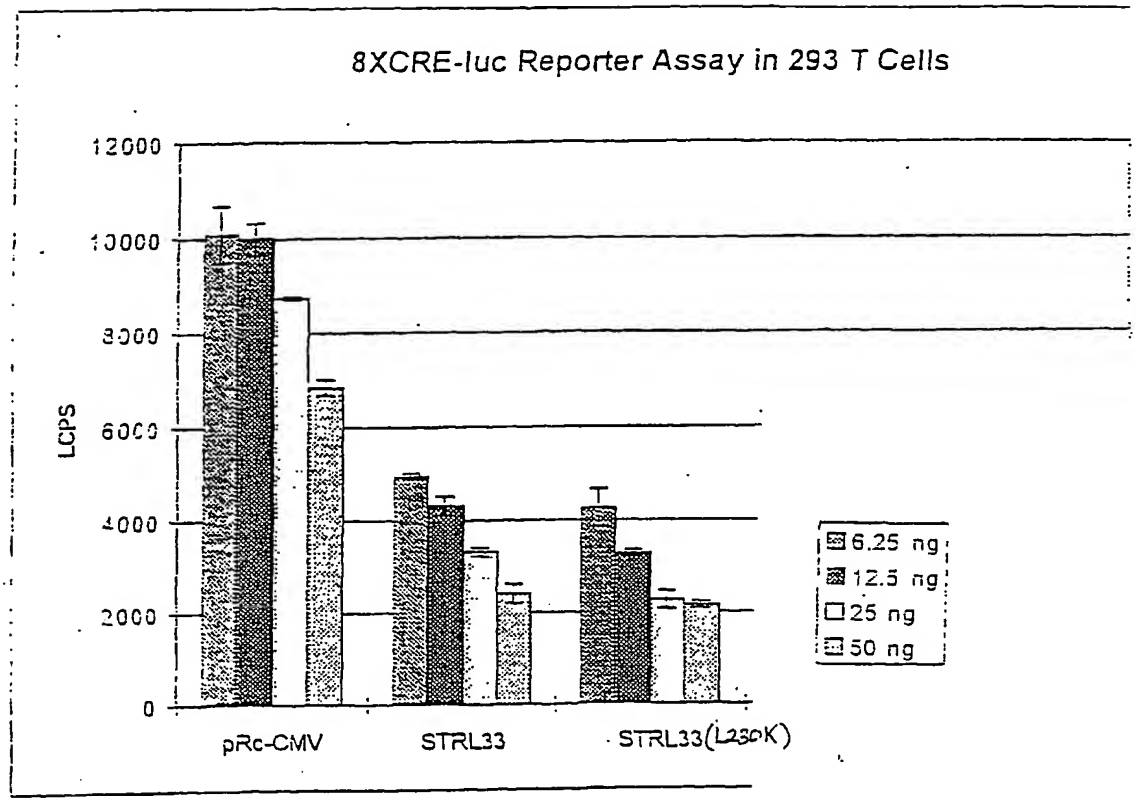

8XCRE-luc Reporter Assay in 293 T Cells
LCPS
12000
10000
8000
6000
4000
2000
0
pRc-CMV
STRL33
STRL33(L230K)
6.25 ng
12.5 ng
25 ng
50 ng

Figure 3

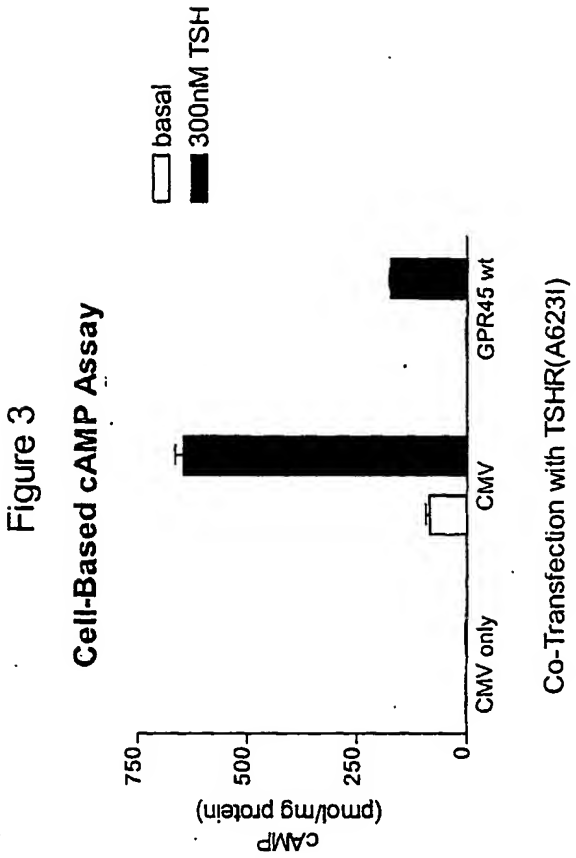
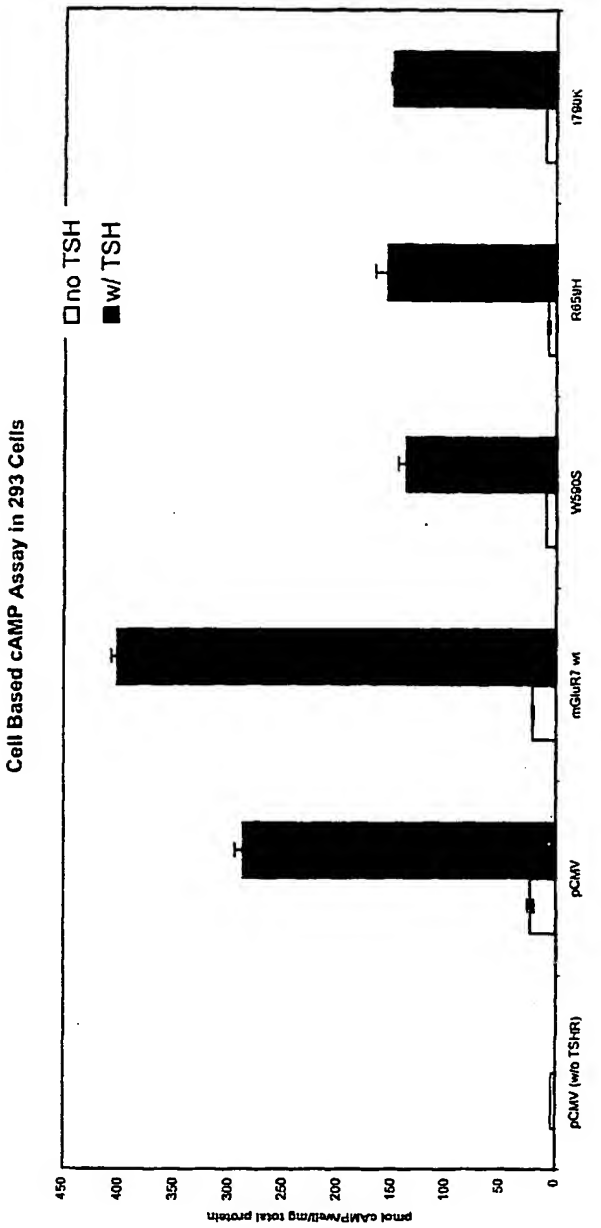

Cell-Based cAMP Assay
basal
300nM TSH
cAMP
(pmol/mg protein)
750
500
250
0
CMV only
CMV
GPR45 wt
Co-Transfection with TSHR(A623I)

Figure 4



Co-Transfection with TSHR(A623I)

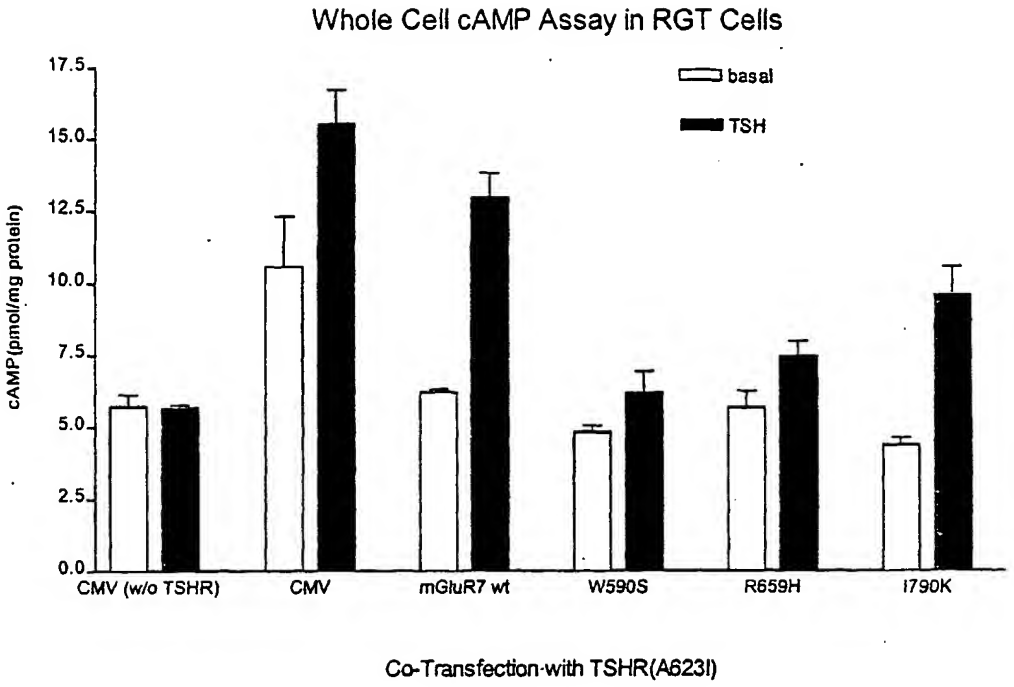

Whole Cell cAMP Assay in RGT Cells
basal
TSH
cAMP(pmol/mg protein)
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
CMV (w/o TSHR)
CMV
mGluR7 wt
W590S
R659H
I790K
Co-Transfection with TSHR(A623I)

Figure 5

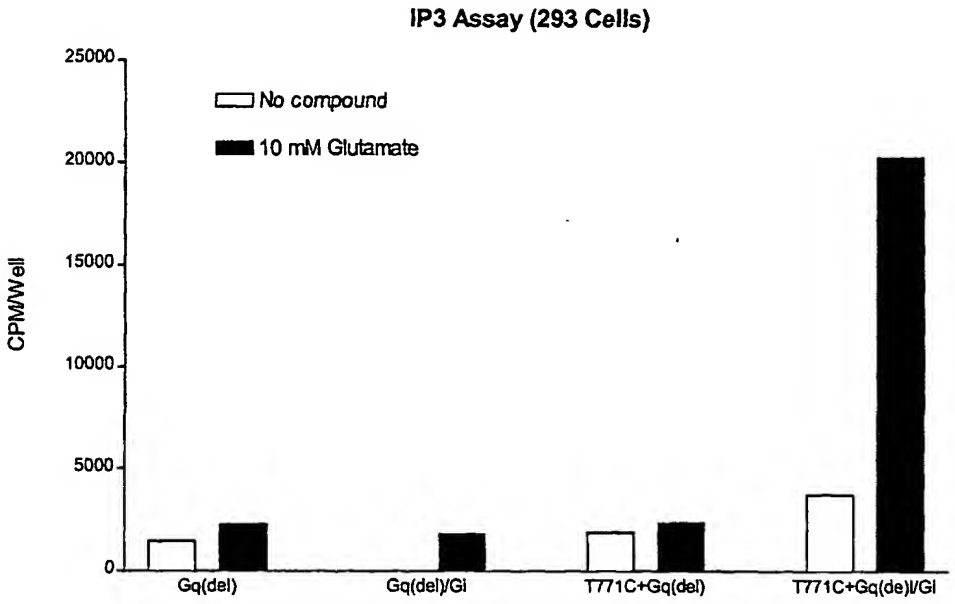

IP3 Assay (293 Cells)
25000
20000
15000
10000
5000
0
CPM/Well
No compound
10 mM Glutamate
Gq(del)
Gq(del)/Gi
T771C+Gq(del)
T771C+Gq(del)I/Gi

Figure 6

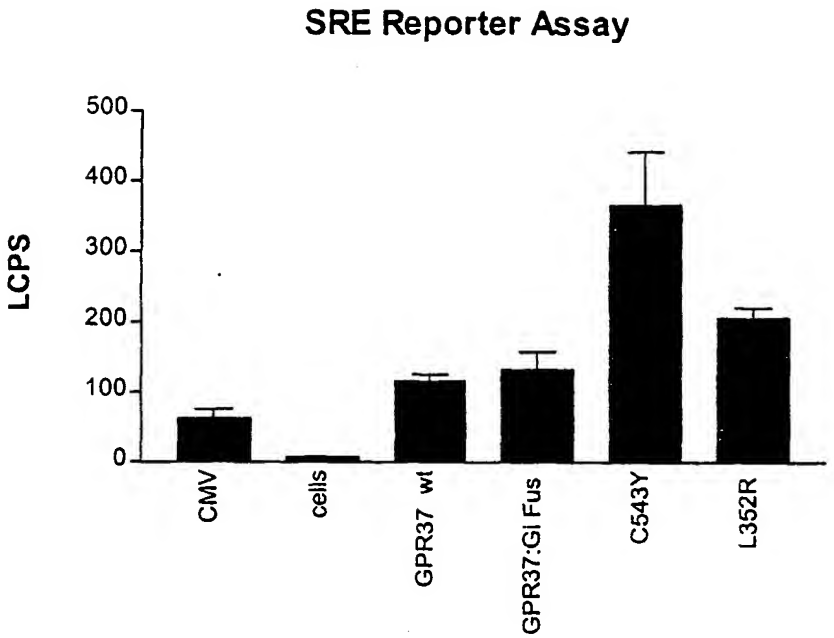

SRE Reporter Assay
LCPS
500
400
300
200
100
0
CMV
cells
GPR37 wt
GPR37:Gi Fus
C543Y
L352R

Figure 7

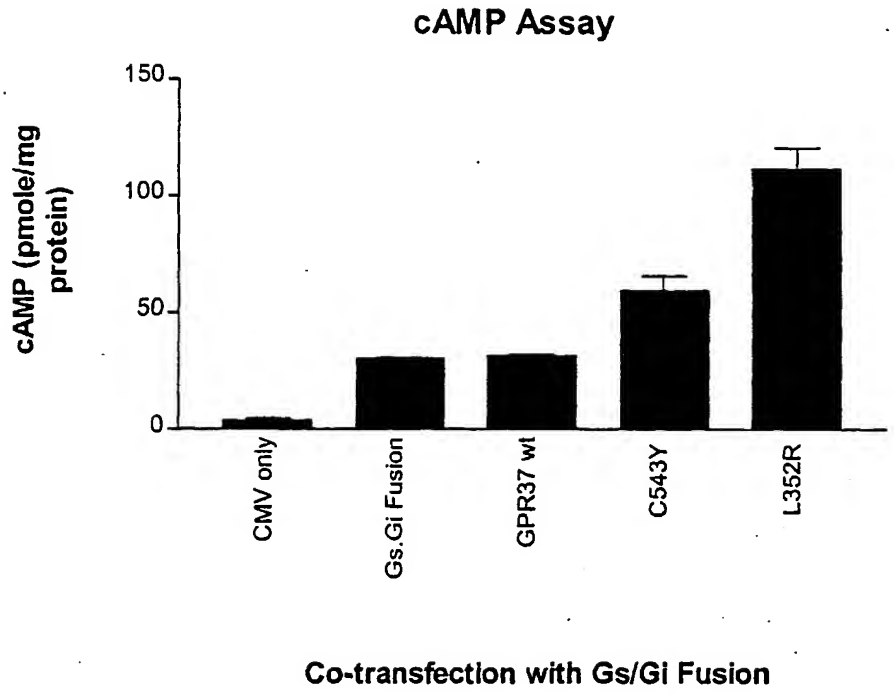

cAMP Assay
cAMP (pmole/mg protein)
150
100
50
0
CMV only
Gs.Gi Fusion
GPR37 wt
C543Y
L352R
Co-transfection with Gs/Gi Fusion

Figure 8

Northern Analysis of GPCR GPR37 expression in forskolin treated Rat Schwann cells

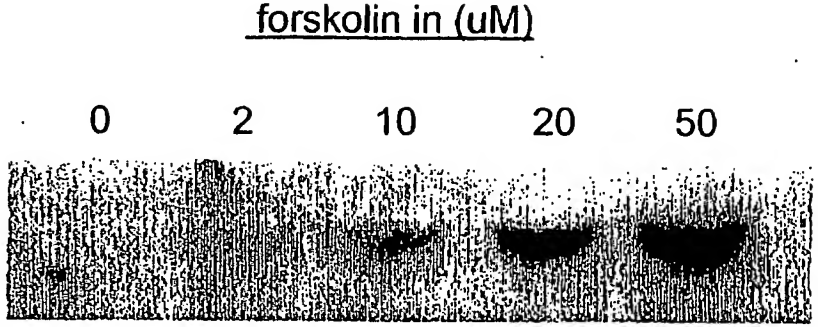


Figure 9

Northern Analysis of GPCR GPR37 Expression in Crushed Rat Sciatic Nerve

Days post-crush

0 1 3 7 10 13

Figure 10

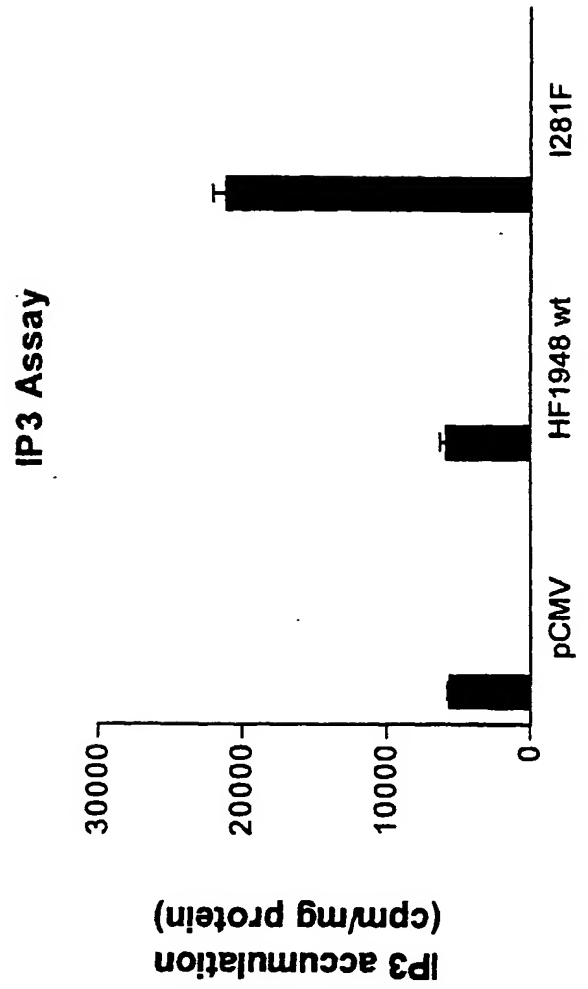

IP3 Assay
IP3 accumulation
(cpm/mg protein)
30000
20000
10000
0
pCMV
HF1948 wt
I281F

Figure 11

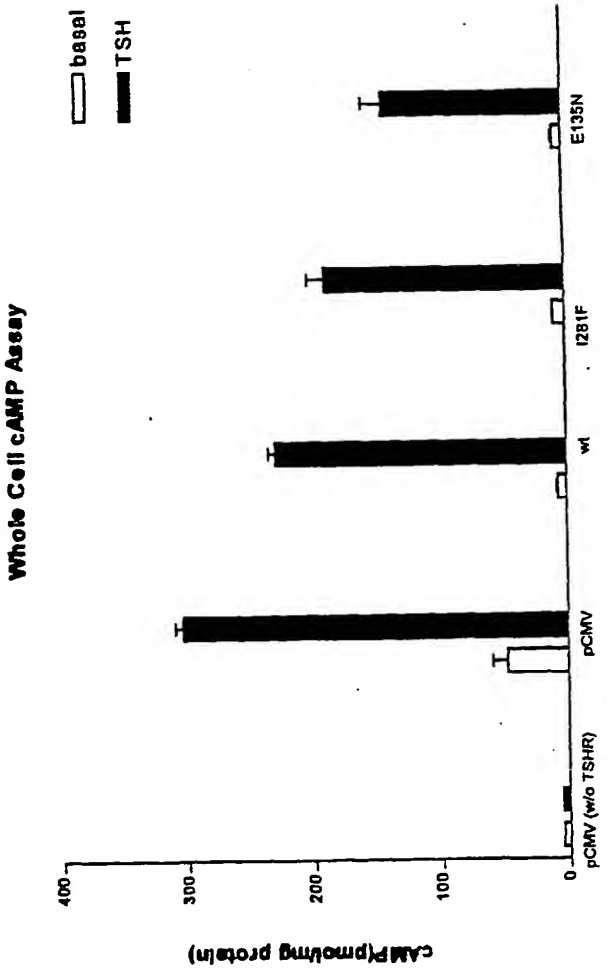
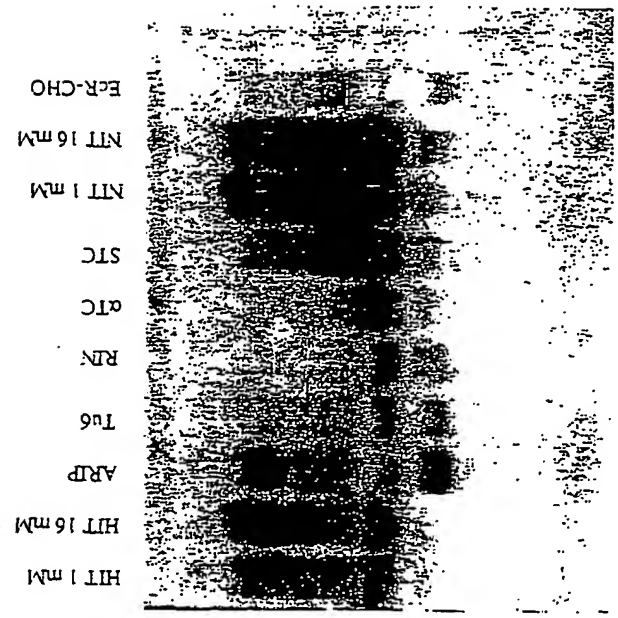

Whole Cell cAMP Assay
basal
TSH
cAMP(pmol/mg protein)
400
300
200
100
0
pCMV (w/o TSHR)
pCMV
wt
I281F
E135N
Co-Transfection With TSHR(A623I)

Figure 12

Figure 13

Cell-specific expression of GPR66 variants in pancreatic cell lines



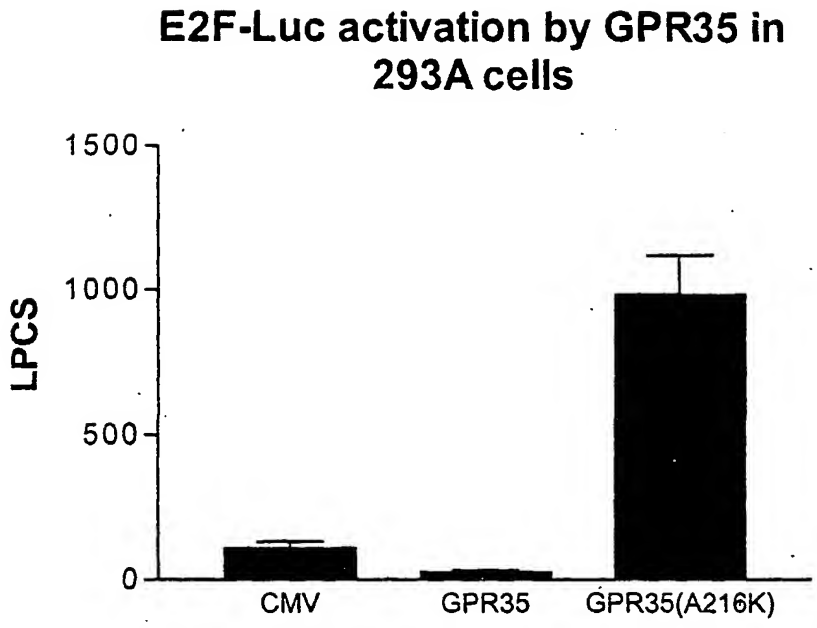
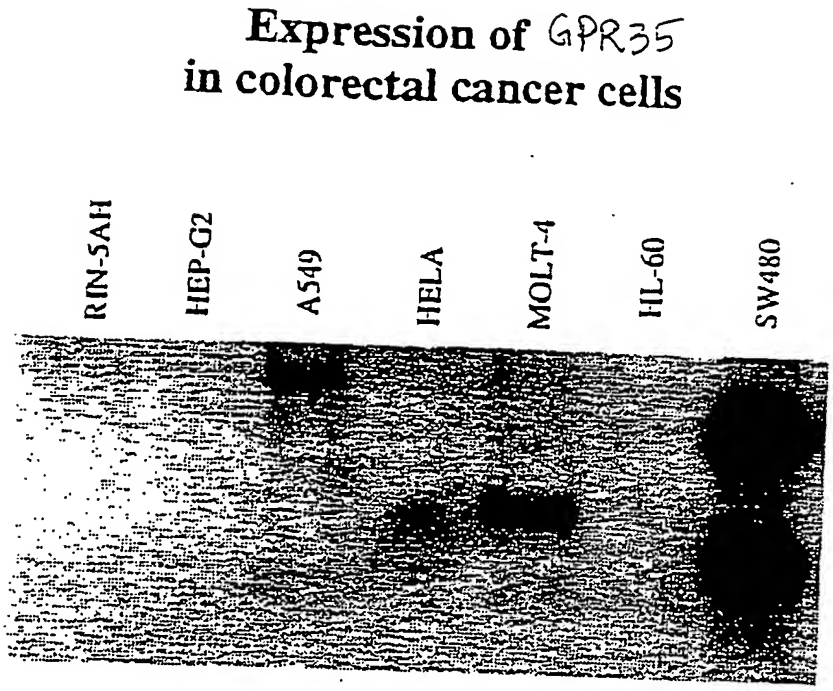
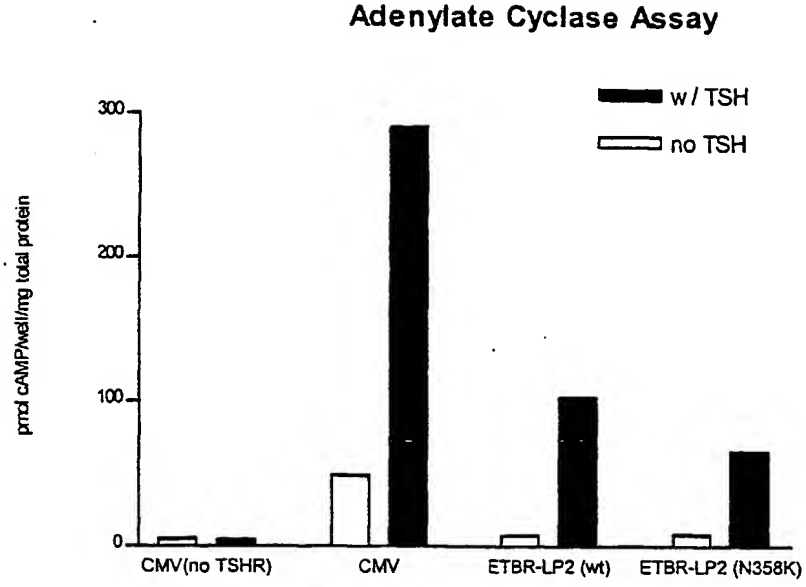

E2F-Luc activation by GPR35 in 293A cells
LPCS
1500
1000
500
0
CMV
GPR35
GPR35(A216K)

Figure 14

Figure 15


Expression of GPR35
in colorectal cancer cells
RIN-5AH
HEP-G2
A549
HELA
MOLT-4
HL-60
SW480



Co-Transfection with TSHR(A623I)

Figure 16

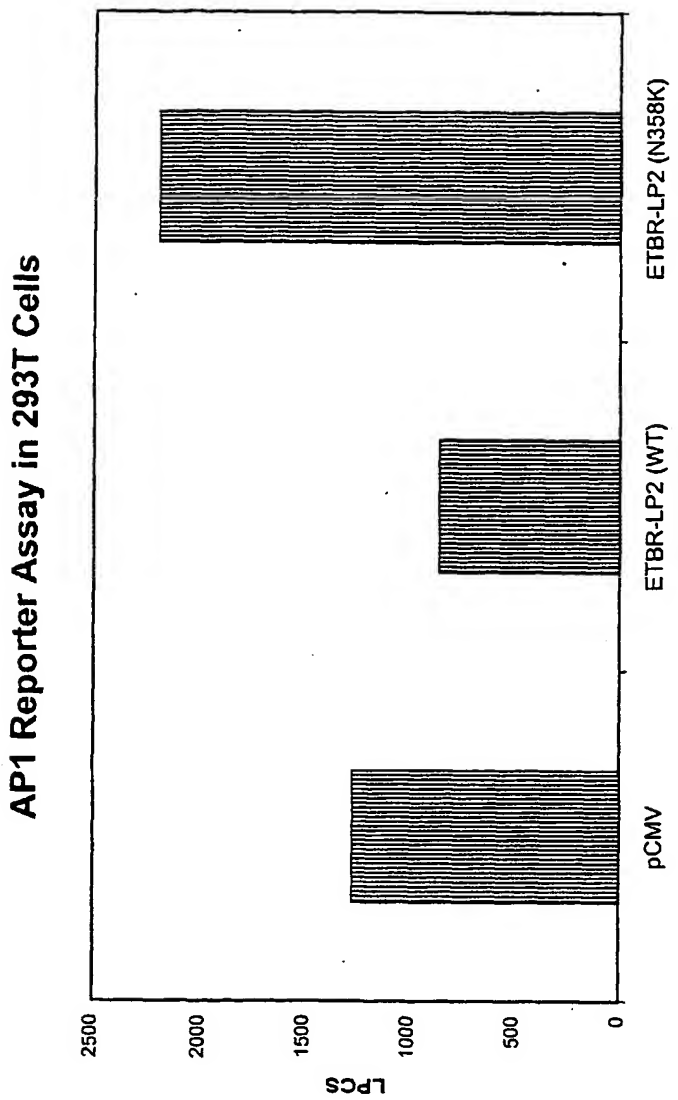

AP1 Reporter Assay in 293T Cells
LPCS
2500
2000
1500
1000
500
0
pCMV
ETBR-LP2 (WT)
ETBR-LP2 (N358K)

Figure 17

Northern Analysis of ETBR-LP2 in Forskolin Treated Rat Schwann Cells

uM Forskolin

0 2 5 10 20 50

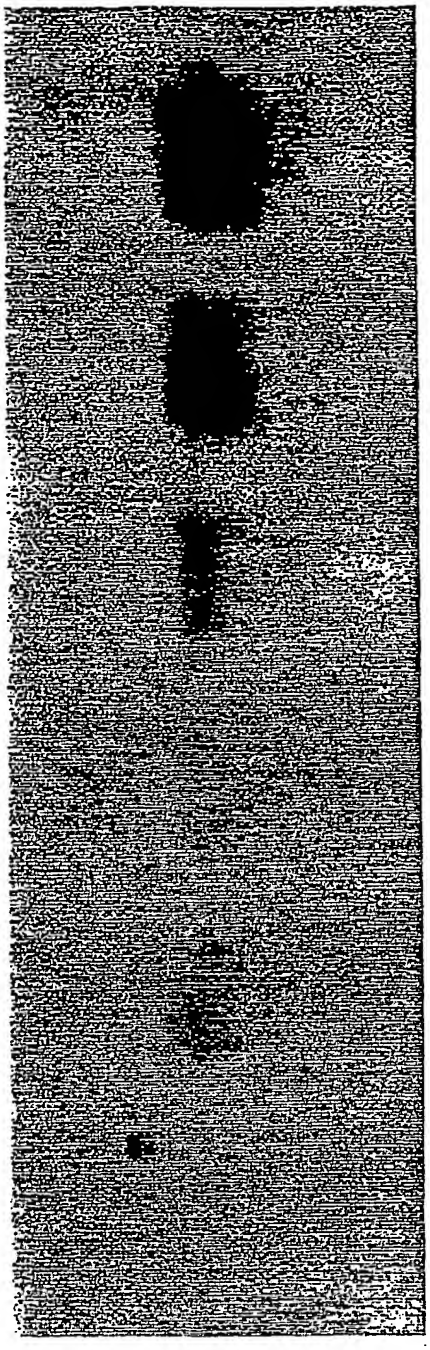


Figure 18

Northern Analysis of ETBR-LP2 Expression in Crushed Rat Sciatic Nerve

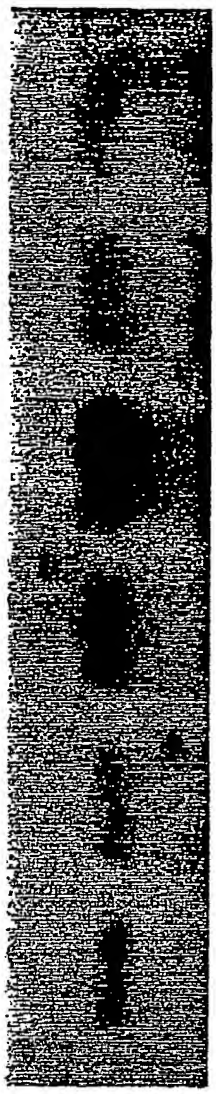


Figure 19

Figure 20A

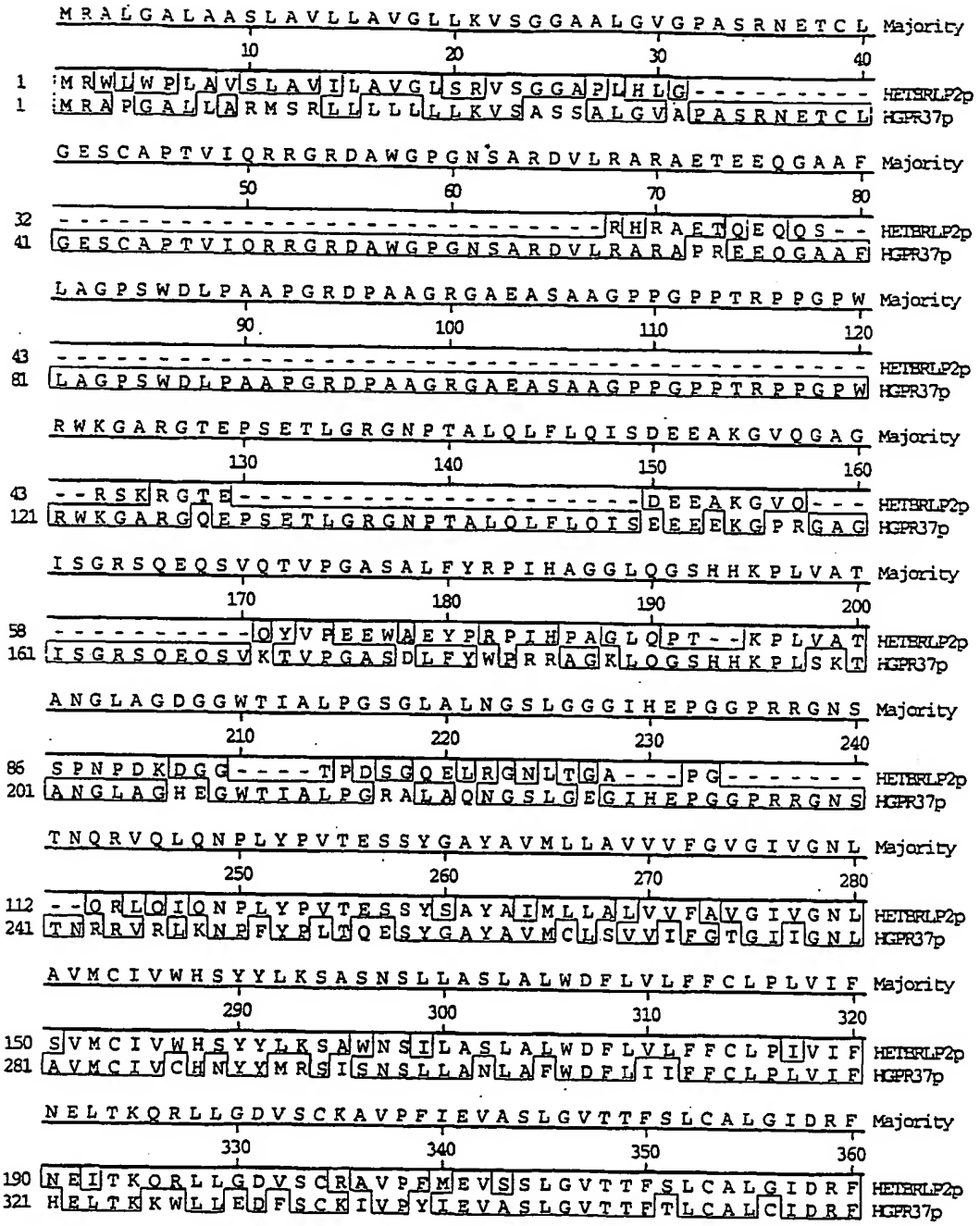
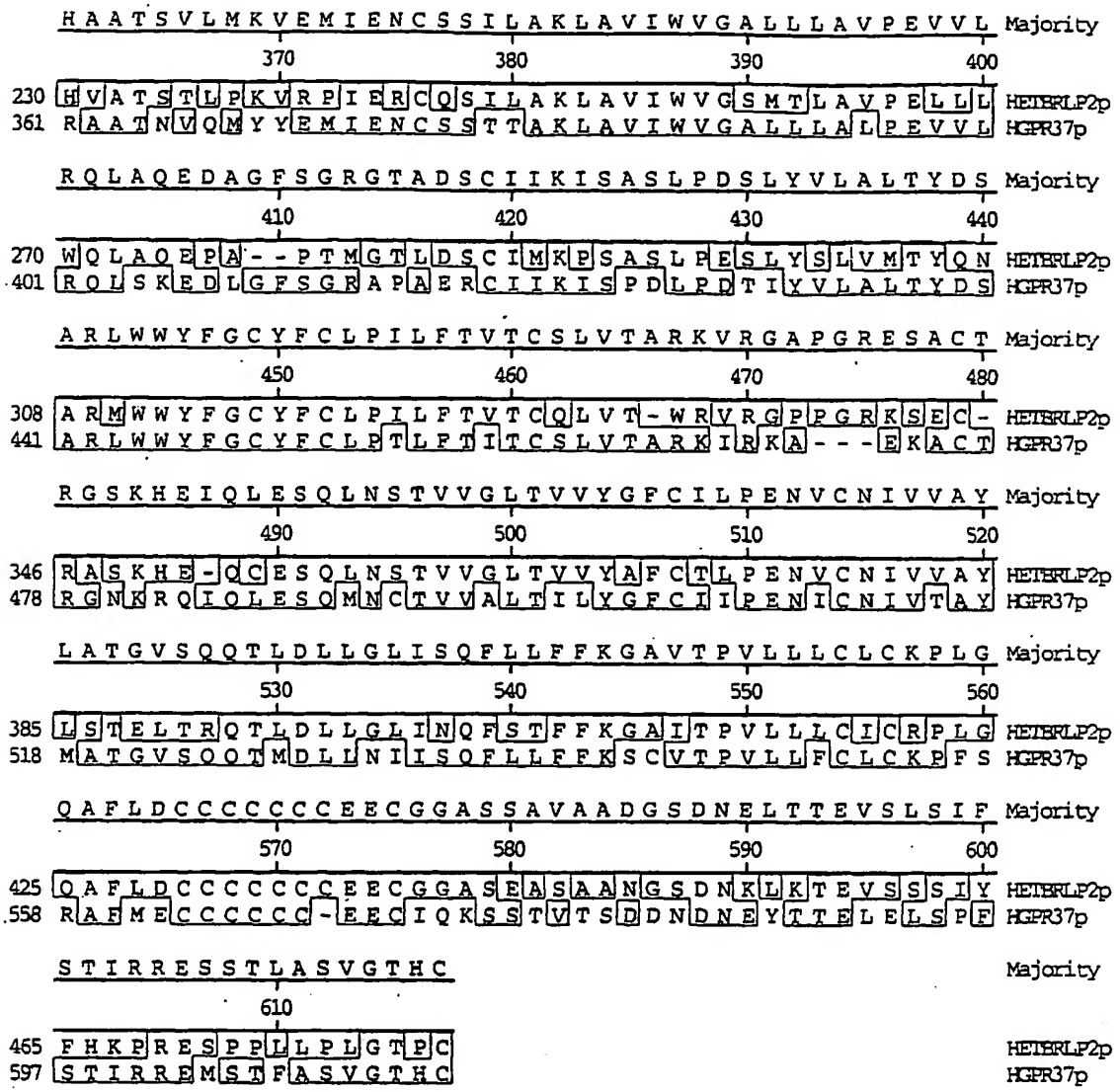

MRALGALAASLAVLLAVGLLKVSGGAALGVGPASRNETCL Majority
10 20 30 40
1 MRWLWPLAVSLAVILAVGLSRVSGGAPLHLG--------- HETERLP2p
1 MRAPGALLARMSRLLLLLLLKVSASSALGVAPASRNETCL HGPR37p
GESCAPTVIQRRGRDAWGPGNSARDVLRARAETEEQGAAF Majority
50 60 70 80
32 ----------RHRAETQEQQS-- HETERLP2p
41 GESCAPTVIQRRGRDAWGPGNSARDVLRARAPREEQGAAF HGPR37p
LAGPSWDLPAAPGRDPAAGRGAEASAAGPPGPPTRPPGPW Majority
90 100 110 120
43 ---------- HETERLP2p
81 LAGPSWDLPAAPGRDPAAGRGAEASAAGPPGPPTRPPGPW HGPR37p
RWKGARGTEPSETLGRGNPTALQLFLQISDEEAKGVQGAG Majority
130 140 150 160
43 --RSKRGTE----------DEEAKGVQ---- HETERLP2p
121 RWKGARGQEPSETLGRGNPTALQLFLQISEEEEKGPRGAG HGPR37p
ISGRSQEQSVQTVPGASALFYRPIHAGGLQGSHHKPLVAT Majority
170 180 190 200
58 ----------QYVPEEWAEYPRPIHPAGLQPT--KPLVAT HETERLP2p
161 ISGRSQEQSVKTVPGASDLFYWERRAGKLQGSHHKPLSKT HGPR37p
ANGLAGDGGWTIALPGSGLALNGSLGGGIHEPGGPRRGNS Majority
210 220 230 240
86 SPNPDKDGG----TPDSGQELRGNLTGA---PG------- HETERLP2p
201 ANGLAGHEGWTIALPGRALAQNGSLGEGIHEPGGPRRGNS HGPR37p
TNQRVQLQNPLYPVTESSYGAYAVMLLAVVVFGVGIVGNL Majority
250 260 270 280
112 --QRLQIQNPLYPVTESSYSAYAIMLLALVVFAVGIVGNL HETERLP2p
241 TNRRVRLKNPFYPLTQESYGAYAVMCLSVVIFGTGIIGNL HGPR37p
AVMCIVWHSYYLKSASNSLLASLALWDFLVLFFCLPLVIF Majority
290 300 310 320
150 SVMCIVWHSYYLKSAWNSILASLALWDFLVLFFCLPIVIF HETERLP2p
281 AVMCIVCHNYYMRSISNSLLANLAFWDFLIIFFCLPLVIF HGPR37p
NELTKQRLLGDVSCKAVPFIEVASLGVTTFSLCALGIDRF Majority
330 340 350 360
190 NEITKQRLLGDVSCRAVPFMEVSSLGVTTFSLCALGIDRF HETERLP2p
321 HELTKKWLLEDFSCKIVPYIEVASLGVTTFTLCALCIDRF HGPR37p

Figure 20B



Decoration 'Decoration #1': Box residues that match the Consensus exactly.

Decoration 'Decoration #2': Box residues that match the Consensus exactly.

SEQUENCE LISTING

<110> Arena Pharmaceuticals, Inc.

<120> Endogenous And Non-Endogenous, Constitutively Activated G Protein-Coupled Receptors

<130> AREN-0321

<160> 102

<170> PatentIn version 3.1

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gtcctgggca atgggcttgt gatctgggtg gctggattcc ggatgacacg cacagtcaac 180

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ctggaccgct gtatttgtgt cctgcatcca gcctgggccc agaaccatcg caccatgagt 420

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ttcatcttct ggactacaat aagtactacg aatggggaca catactgtat tttcaacttt 540

gcattctggg gtgacactgc tgtagagagg ttgaacgtgt tcattaccat ggccaaggtc 600

tttctgatcc tccacttcat tattggcttc agcgtgccta tgtccatcat cacagtctgc 660

tatgggatca tcgctgccaa aattcacaga aaccacatga ttaaatccag ccgtccctta 720

cgtgtcttcg ctgctgtggt ggcttctttc ttcatctgtt ggttccctta tgaactaatt 780

ggcattctaa tggcagtctg gctcaaagag atgttgttaa atggcaaata caaaatcatt 840

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ctctacgtct ttatgggtcg taacttccaa gaaagactga ttcgctcttt gcccactagt 960

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<210> 2
<211> 353
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<213> Homo sapiens

<400> 2

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Pro Glu Pro Ala Gly His Thr Val Leu Trp Ile Phe Ser Leu Leu Val
20 25 30

His Gly Val Thr Phe Val Phe Gly Val Leu Gly Asn Gly Leu Val Ile
35 40 45

Trp Val Ala Gly Phe Arg Met Thr Arg Thr Val Asn Thr Ile Cys Tyr
50 55 60

Leu Asn Leu Ala Leu Ala Asp Phe Ser Phe Ser Ala Ile Leu Pro Phe
65 70 75 80

Arg Met Val Ser Val Ala Met Arg Glu Lys Trp Pro Phe Gly Ser Phe
85 90 95

Leu Cys Lys Leu Val His Val Met Ile Asp Ile Asn Leu Phe Val Ser
100 105 110

Val Tyr Leu Ile Thr Ile Ile Ala Leu Asp Arg Cys Ile Cys Val Leu
115 120 125

His Pro Ala Trp Ala Gln Asn His Arg Thr Met Ser Leu Ala Lys Arg
130 135 140

Val Met Thr Gly Leu Trp Ile Phe Thr Ile Val Leu Thr Leu Pro Asn
145 150 155 160

Phe Ile Phe Trp Thr Thr Ile Ser Thr Thr Asn Gly Asp Thr Tyr Cys
165 170 175

Ile Phe Asn Phe Ala Phe Trp Gly Asp Thr Ala Val Glu Arg Leu Asn
180 185 190

Val Phe Ile Thr Met Ala Lys Val Phe Leu Ile Leu His Phe Ile Ile
195 200 205

Gly Phe Ser Val Pro Met Ser Ile Ile Thr Val Cys Tyr Gly Ile Ile
210 215 220

Ala Ala Lys Ile His Arg Asn His Met Ile Lys Ser Ser Arg Pro Leu
225 230 235 240

Arg Val Phe Ala Ala Val Val Ala Ser Phe Phe Ile Cys Trp Phe Pro
245 250 255

Tyr Glu Leu Ile Gly Ile Leu Met Ala Val Trp Leu Lys Glu Met Leu
260 265 270

Leu Asn Gly Lys Tyr Lys Ile Ile Leu Val Leu Ile Asn Pro Thr Ser
275 280 285

Ser Leu Ala Phe Phe Asn Ser Cys Leu Asn Pro Ile Leu Tyr Val Phe
290 295 300

Met Gly Arg Asn Phe Gln Glu Arg Leu Ile Arg Ser Leu Pro Thr Ser
305 310 315 320

Leu Glu Arg Ala Leu Thr Glu Val Pro Asp Ser Ala Gln Thr Ser Asn
325 330 335

Thr Asp Thr Thr Ser Ala Ser Pro Pro Glu Glu Thr Glu Leu Gln Ala
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Met

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<211> 1029
<212> DNA
<213> Homo sapiens

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gtgtttgtct gtggtctggt ggggaactct ctggtgctgg tcatatccat cttctaccat 180

aagttgcaga gcctgacgga tgtgttcctg gtgaacctac ccctggctga cctggtgttt 240

gtctgcactc tgcccttctg ggcctatgca ggcatccatg aatgggtgtt tggccaggtc 300

atgtgcaaaa gcctactggg catctacact attaacttct acacgtccat gctcatcctc 360

acctgcatca ctgtggatcg tttcattgta gtggttaagg ccaccaaggc ctacaaccag 420

caagccaaga ggatgacctg gggcaaggtc accagcttgc tcatctgggt gatatccctg 480

ctggtttcct tgccccaaat tatctatggc aatgtcttta atctcgacaa gctcatatgt 540

ggttaccatg acgaggcaat ttccactgtg gttcttgcca cccagatgac actggggttc 600

ttcttgccac tgctcaccat gattgtctgc tattcagtca taatcaaaac actgcttcat 660

gctggaggct tccagaagca cagatctcta aagatcatct tcctggtgat ggctgtgttc 720

ctgctgaccc agatgcccct caacctcatg aagttcatcc gcagcacaca ctgggaatac 780

tatgccatga ccagctttca ctacaccatc atggtgacag aggccatcgc atacctgagg 840

gcctgcctta accctgtgct ctatgccttt gtcagcctga agtttcgaaa gaacttctgg 900

aaacttgtga aggacattgg ttgcctccct taccttgggg tctcacatca atggaaatct 960

tctgaggaca attccaagac tttttctgcc tcccacaatg tggaggccac cagcatgttc 1020

cagttatag 1029

<210> 4
<211> 342
<212> PRT
<213> Homo sapiens

<400> 4

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1 5 10 15

Asp Ser Ser Gln Glu Glu His Gln Ala Phe Leu Gln Phe Ser Lys Val
20 25 30

Phe Leu Pro Cys Met Tyr Leu Val Val Phe Val Cys Gly Leu Val Gly
35 40 45

Asn Ser Leu Val Leu Val Ile Ser Ile Phe Tyr His Lys Leu Gln Ser
50 55 60

Leu Thr Asp Val Phe Leu Val Asn Leu Pro Leu Ala Asp Leu Val Phe
65 70 75 80

Val Cys Thr Leu Pro Phe Trp Ala Tyr Ala Gly Ile His Glu Trp Val
85 90 95

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Phe Gly Gln Val Met Cys Lys Ser Leu Leu Gly Ile Tyr Thr Ile Asn
            100                 105                 110

Phe Tyr Thr Ser Met Leu Ile Leu Thr Cys Ile Thr Val Asp Arg Phe
        115                 120                 125

Ile Val Val Val Lys Ala Thr Lys Ala Tyr Asn Gln Gln Ala Lys Arg
    130                 135                 140

Met Thr Trp Gly Lys Val Thr Ser Leu Leu Ile Trp Val Ile Ser Leu
145                 150                 155                 160

Leu Val Ser Leu Pro Gln Ile Ile Tyr Gly Asn Val Phe Asn Leu Asp
                165                 170                 175

Lys Leu Ile Cys Gly Tyr His Asp Glu Ala Ile Ser Thr Val Val Leu
            180                 185                 190

Ala Thr Gln Met Thr Leu Gly Phe Phe Leu Pro Leu Leu Thr Met Ile
        195                 200                 205

Val Cys Tyr Ser Val Ile Ile Lys Thr Leu Leu His Ala Gly Gly Phe
    210                 215                 220

Gln Lys His Arg Ser Leu Lys Ile Ile Phe Leu Val Met Ala Val Phe
225                 230                 235                 240

Leu Leu Thr Gln Met Pro Phe Asn Leu Met Lys Phe Ile Arg Ser Thr
                245                 250                 255

His Trp Glu Tyr Tyr Ala Met Thr Ser Phe His Tyr Thr Ile Met Val
            260                 265                 270

Thr Glu Ala Ile Ala Tyr Leu Arg Ala Cys Leu Asn Pro Val Leu Tyr
        275                 280                 285

Ala Phe Val Ser Leu Lys Phe Arg Lys Asn Phe Trp Lys Leu Val Lys
    290                 295                 300

Asp Ile Gly Cys Leu Pro Tyr Leu Gly Val Ser His Gln Trp Lys Ser
305                 310                 315                 320
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Ser Glu Asp Asn Ser Lys Thr Phe Ser Ala Ser His Asn Val Glu Ala
325 330 335

Thr Ser Met Phe Gln Leu
340

<210> 5
<211> 1119
<212> DNA
<213> Homo sapiens

<400> 5
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gcctcagact cggggtccac ccagttgccc gcacccctca ggatctcctt ggccatagtg 120

atgctgctga tgaccgtggt ggggttcctg ggcaacactg tggtctgcat catcgtgtac 180

cagaggccgg ctatgcgctc ggccatcaac ctgctgctgg ccaccctggc cttctccgac 240

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cactttgggg accacttctg ccgcctctca gccacgctct actggttttt tgtcctggag 360

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gacaagctga acccgcgcag ggccaaggtg atcatcgcgg tctcctgggt gctgtccttc 480

tgcatcgcgg ggccctcgct cacgggctgg acgctggtgg aggtgccggc gcgggcccca 540

cagtgcgtgc tgggctacac ggagctcccc gctgaccgcg catacgtggt caccttggtg 600

gtggccgtgt tcttcgcgcc ctttggcgtc atgctgtgcg cctacatgtg catcctcaac 660

acggtccgca agaacgccgt gcgcgtgcac aaccagtcgg acagcctgga cctgcggcag 720

ctcaccaggg cgggcctgcg gcgcctgcag cggcagcaac aggtcagcgt ggacttgagc 780

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<212> PRT

<213> Homo sapiens

<400> 6

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            20                  25                  30

Leu Arg Ile Ser Leu Ala Ile Val Met Leu Leu Met Thr Val Val Gly
        35                  40                  45

Phe Leu Gly Asn Thr Val Val Cys Ile Ile Val Tyr Gln Arg Pro Ala
    50                  55                  60

Met Arg Ser Ala Ile Asn Leu Leu Leu Ala Thr Leu Ala Phe Ser Asp
65                  70                  75                  80

Ile Met Leu Ser Leu Cys Cys Met Pro Phe Thr Ala Val Thr Leu Ile
                85                  90                  95

Thr Val Arg Trp His Phe Gly Asp His Phe Cys Arg Leu Ser Ala Thr
            100                 105                 110

Leu Tyr Trp Phe Phe Val Leu Glu Gly Val Ala Ile Leu Leu Ile Ile
        115                 120                 125

Ser Val Asp Arg Phe Leu Ile Ile Val Gln Arg Gln Asp Lys Leu Asn
    130                 135                 140

Pro Arg Arg Ala Lys Val Ile Ile Ala Val Ser Trp Val Leu Ser Phe
145                 150                 155                 160

Cys Ile Ala Gly Pro Ser Leu Thr Gly Trp Thr Leu Val Glu Val Pro
                165                 170                 175

Ala Arg Ala Pro Gln Cys Val Leu Gly Tyr Thr Glu Leu Pro Ala Asp
            180                 185                 190

Arg Ala Tyr Val Val Thr Leu Val Val Ala Val Phe Phe Ala Pro Phe
        195                 200                 205

Gly Val Met Leu Cys Ala Tyr Met Cys Ile Leu Asn Thr Val Arg Lys
```

210 215 220

Asn Ala Val Arg Val His Asn Gln Ser Asp Ser Leu Asp Leu Arg Gln
225 230 235 240

Leu Thr Arg Ala Gly Leu Arg Arg Leu Gln Arg Gln Gln Gln Val Ser
245 250 255

Val Asp Leu Ser Phe Lys Thr Lys Ala Phe Thr Thr Ile Leu Ile Leu
260 265 270

Phe Val Gly Phe Ser Leu Cys Trp Leu Pro His Ser Val Tyr Ser Leu
275 280 285

Leu Ser Val Phe Ser Gln Arg Phe Tyr Cys Gly Ser Ser Phe Tyr Ala
290 295 300

Thr Ser Thr Cys Val Leu Trp Phe Ser Tyr Leu Lys Ser Val Phe Asn
305 310 315 320

Pro Ile Val Tyr Cys Trp Arg Ile Lys Lys Phe Arg Glu Ala Cys Ile
325 330 335

Glu Leu Leu Pro Gln Thr Phe Gln Ile Leu Pro Lys Val Pro Glu Arg
340 345 350

Ile Arg Arg Arg Ile Gln Pro Ser Thr Val Tyr Val Cys Asn Glu Asn
355 360 365

Gln Ser Ala Val
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<210> 7
<211> 2748
<212> DNA
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cactcaatcc ggatcgaggg ggacgtcacc ctcgggggggc tgttccccgt gcacgccaag 180

ggtcccagcg gagtgccctg cggcgacatc aagagggaaa acgggatcca caggctggaa 240

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<213> Homo sapiens

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20 25 30

Arg Gly Gln Glu Met Tyr Ala Pro His Ser Ile Arg Ile Glu Gly Asp
35 40 45

Val Thr Leu Gly Gly Leu Phe Pro Val His Ala Lys Gly Pro Ser Gly
50 55 60

Val Pro Cys Gly Asp Ile Lys Arg Glu Asn Gly Ile His Arg Leu Glu
65 70 75 80

Ala Met Leu Tyr Ala Leu Asp Gln Ile Asn Ser Asp Pro Asn Leu Leu
85 90 95

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Pro Asn Val Thr Leu Gly Ala Arg Ile Leu Asp Thr Cys Ser Arg Asp
            100                 105                 110

Thr Tyr Ala Leu Glu Gln Ser Leu Thr Phe Val Gln Ala Leu Ile Gln
        115                 120                 125

Lys Asp Thr Ser Asp Val Arg Cys Thr Asn Gly Glu Pro Pro Val Phe
    130                 135                 140

Val Lys Pro Glu Lys Val Val Gly Val Ile Gly Ala Ser Gly Ser Ser
145                 150                 155                 160

Val Ser Ile Met Val Ala Asn Ile Leu Arg Leu Phe Gln Ile Pro Gln
                165                 170                 175

Ile Ser Tyr Ala Ser Thr Ala Pro Glu Leu Ser Asp Asp Arg Arg Tyr
            180                 185                 190

Asp Phe Phe Ser Arg Val Val Pro Pro Asp Ser Phe Gln Ala Gln Ala
        195                 200                 205

Met Val Asp Ile Val Lys Ala Leu Gly Trp Asn Tyr Val Ser Thr Leu
    210                 215                 220

Ala Ser Glu Gly Ser Tyr Gly Glu Lys Gly Val Glu Ser Phe Thr Gln
225                 230                 235                 240

Ile Ser Lys Glu Ala Gly Gly Leu Cys Ile Ala Gln Ser Val Arg Ile
                245                 250                 255

Pro Gln Glu Arg Lys Asp Arg Thr Ile Asp Phe Asp Arg Ile Ile Lys
            260                 265                 270

Gln Leu Leu Asp Thr Pro Asn Ser Arg Ala Val Val Ile Phe Ala Asn
        275                 280                 285

Asp Glu Asp Ile Lys Gln Ile Leu Ala Ala Ala Lys Arg Ala Asp Gln
    290                 295                 300

Val Gly His Phe Leu Trp Val Gly Ser Asp Ser Trp Gly Ser Lys Ile
305                 310                 315                 320
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Asn Pro Leu His Gln His Glu Asp Ile Ala Glu Gly Ala Ile Thr Ile
                325                 330                 335

Gln Pro Lys Arg Ala Thr Val Glu Gly Phe Asp Ala Tyr Phe Thr Ser
            340                 345                 350

Arg Thr Leu Glu Asn Asn Arg Arg Asn Val Trp Phe Ala Glu Tyr Trp
        355                 360                 365

Glu Glu Asn Phe Asn Cys Lys Leu Thr Ile Ser Gly Ser Lys Lys Glu
    370                 375                 380

Asp Thr Asp Arg Lys Cys Thr Gly Gln Glu Arg Ile Gly Lys Asp Ser
385                 390                 395                 400

Asn Tyr Glu Gln Glu Gly Lys Val Gln Phe Val Ile Asp Ala Val Tyr
                405                 410                 415

Ala Met Ala His Ala Leu His His Met Asn Lys Asp Leu Cys Ala Asp
            420                 425                 430

Tyr Arg Gly Val Cys Pro Glu Met Glu Gln Ala Gly Gly Lys Lys Leu
        435                 440                 445

Leu Lys Tyr Ile Arg Asn Val Asn Phe Asn Gly Ser Ala Gly Thr Pro
    450                 455                 460

Val Met Phe Asn Lys Asn Gly Asp Ala Pro Gly Arg Tyr Asp Ile Phe
465                 470                 475                 480

Gln Tyr Gln Thr Thr Asn Thr Ser Asn Pro Gly Tyr Arg Leu Ile Gly
                485                 490                 495

Gln Trp Thr Asp Glu Leu Gln Leu Asn Ile Glu Asp Met Gln Trp Gly
            500                 505                 510

Lys Gly Val Arg Glu Ile Pro Ala Ser Val Cys Thr Leu Pro Cys Lys
        515                 520                 525

Pro Gly Gln Arg Lys Lys Thr Gln Lys Gly Thr Pro Cys Cys Trp Thr
    530                 535                 540
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Cys Glu Pro Cys Asp Gly Tyr Gln Tyr Gln Phe Asp Glu Met Thr Cys
545                 550                 555                 560

Gln His Cys Pro Tyr Asp Gln Arg Pro Asn Glu Asn Arg Thr Gly Cys
                565                 570                 575

Gln Asp Ile Pro Ile Ile Lys Leu Glu Trp His Ser Pro Trp Ala Val
            580                 585                 590

Ile Pro Val Phe Leu Ala Met Leu Gly Ile Ile Ala Thr Ile Phe Val
        595                 600                 605

Met Ala Thr Phe Ile Arg Tyr Asn Asp Thr Pro Ile Val Arg Ala Ser
    610                 615                 620

Gly Arg Glu Leu Ser Tyr Val Leu Leu Thr Gly Ile Phe Leu Cys Tyr
625                 630                 635                 640

Ile Ile Thr Phe Leu Met Ile Ala Lys Pro Asp Val Ala Val Cys Ser
                645                 650                 655

Phe Arg Arg Val Phe Leu Gly Leu Gly Met Cys Ile Ser Tyr Ala Ala
            660                 665                 670

Leu Leu Thr Lys Thr Asn Arg Ile Tyr Arg Ile Phe Glu Gln Gly Lys
        675                 680                 685

Lys Ser Val Thr Ala Pro Arg Leu Ile Ser Pro Thr Ser Gln Leu Ala
    690                 695                 700

Ile Thr Ser Ser Leu Ile Ser Val Gln Leu Leu Gly Val Phe Ile Trp
705                 710                 715                 720

Phe Gly Val Asp Pro Pro Asn Ile Ile Ile Asp Tyr Asp Glu His Lys
                725                 730                 735

Thr Met Asn Pro Glu Gln Ala Arg Gly Val Leu Lys Cys Asp Ile Thr
            740                 745                 750

Asp Leu Gln Ile Ile Cys Ser Leu Gly Tyr Ser Ile Leu Leu Met Val
        755                 760                 765

Thr Cys Thr Val Tyr Ala Ile Lys Thr Arg Gly Val Pro Glu Asn Phe
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770 775 780

Asn Glu Ala Lys Pro Ile Gly Phe Thr Met Tyr Thr Thr Cys Ile Val
785 790 795 800

Trp Leu Ala Phe Ile Pro Ile Phe Phe Gly Thr Ala Gln Ser Ala Glu
805 810 815

Lys Leu Tyr Ile Gln Thr Thr Thr Leu Thr Ile Ser Met Asn Leu Ser
820 825 830

Ala Ser Val Ala Leu Gly Met Leu Tyr Met Pro Lys Val Tyr Ile Ile
835 840 845

Ile Phe His Pro Glu Leu Asn Val Gln Lys Arg Lys Arg Ser Phe Lys
850 855 860

Ala Val Val Thr Ala Ala Thr Met Ser Ser Arg Leu Ser His Lys Pro
865 870 875 880

Ser Asp Arg Pro Asn Gly Glu Ala Lys Thr Glu Leu Cys Glu Asn Val
885 890 895

Asp Pro Asn Ser Pro Ala Ala Lys Lys Lys Tyr Val Ser Tyr Asn Asn
900 905 910

Leu Val Ile
915

<210> 9
<211> 1842
<212> DNA
<213> Homo sapiens

<400> 9
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ggggagagct gtgcacctac agtgatccag cgccgcggca gggacgcctg gggaccggga 180

aattctgcaa gagacgttct gcgagcccga gcacccaggg aggagcaggg ggcagcgttt 240

cttgcgggac cctcctggga cctgccggcg gccccgggcc gtgacccggc tgcaggcaga 300

ggggcggagg cgtcggcagc cggacccccg ggacctccaa ccaggccacc tggcccctgg 360

aggtggaaag gtgctcgggg tcaggagcct tctgaaactt tggggagagg gaaccccacg 420

gccctccagc tcttccttca gatctcagag gaggaagaga agggtcccag aggcgctggc 480

atttccgggc gtagccagga gcagagtgtg aagacagtcc ccggagccag cgatcttttt 540

tactggccaa ggagagccgg gaaactccag ggttcccacc acaagcccct gtccaagacg 600

gccaatggac tggcggggca cgaagggtgg acaattgcac tcccgggccg ggcgctggcc 660

cagaatggat ccttgggtga aggaatccat gagcctgggg gtccccgccg gggaaacagc 720

acgaaccggc gtgtgagact gaagaacccc ttctacccgc tgacccagga gtcctatgga 780

gcctacgcgg tcatgtgtct gtccgtggtg atcttcggga ccggcatcat tggcaacctg 840

gcggtgatgt gcatcgtgtg ccacaactac tacatgcgga gcatctccaa ctccctcttg 900

gccaacctgg ccttctggga ctttctcatc atcttcttct gccttccgct ggtcatcttc 960

cacgagctga ccaagaagtg gctgctggag gacttctcct gcaagatcgt gccctatata 1020

gaggtcgctt ctctgggagt caccaccttc accttatgtg ctctgtgcat agaccgcttc 1080

cgtgctgcca ccaacgtaca gatgtactac gaaatgatcg aaaactgttc ctcaacaact 1140

gccaaacttg ctgttatatg ggtgggagct ctattgttag cacttccaga agttgttctc 1200

cgccagctga gcaaggagga tttggggttt agtggccgag ctccggcaga aaggtgcatt 1260

attaagatct ctcctgattt accagacacc atctatgttc tagccctcac ctacgacagt 1320

gcgagactgt ggtggtattt tggctgttac ttttgtttgc ccacgctttt caccatcacc 1380

tgctctctag tgactgcgag gaaaatccgc aaagcagaga aagcctgtac ccgagggaat 1440

aaacggcaga ttcaactaga gagtcagatg aactgtacag tagtggcact gaccatttta 1500

tatggatttt gcattattcc tgaaaatatc tgcaacattg ttactgccta catggctaca 1560

ggggtttcac agcagacaat ggacctcctt aatatcatca gccagttcct tttgttcttt 1620

aagtcctgtg tcaccccagt cctccttttc tgtctctgca aacccttcag tcgggccttc 1680

atggagtgct gctgctgttg ctgtgaggaa tgcattcaga agtcttcaac ggtgaccagt 1740

gatgacaatg acaacgagta caccacggaa ctcgaactct cgcctttcag taccatacgc 1800

cgtgaaatgt ccacttttgc ttctgtcgga actcattgct ga 1842

<210> 10
<211> 613
<212> PRT
<213> Homo sapiens

<400> 10

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Met Arg Ala Pro Gly Ala Leu Leu Ala Arg Met Ser Arg Leu Leu Leu
1               5                  10                  15

Leu Leu Leu Leu Lys Val Ser Ala Ser Ser Ala Leu Gly Val Ala Pro
            20                  25                  30

Ala Ser Arg Asn Glu Thr Cys Leu Gly Glu Ser Cys Ala Pro Thr Val
        35                  40                  45

Ile Gln Arg Arg Gly Arg Asp Ala Trp Gly Pro Gly Asn Ser Ala Arg
    50                  55                  60

Asp Val Leu Arg Ala Arg Ala Pro Arg Glu Glu Gln Gly Ala Ala Phe
65                  70                  75                  80

Leu Ala Gly Pro Ser Trp Asp Leu Pro Ala Ala Pro Gly Arg Asp Pro
                85                  90                  95

Ala Ala Gly Arg Gly Ala Glu Ala Ser Ala Ala Gly Pro Pro Gly Pro
            100                 105                 110

Pro Thr Arg Pro Pro Gly Pro Trp Arg Trp Lys Gly Ala Arg Gly Gln
        115                 120                 125

Glu Pro Ser Glu Thr Leu Gly Arg Gly Asn Pro Thr Ala Leu Gln Leu
    130                 135                 140

Phe Leu Gln Ile Ser Glu Glu Glu Glu Lys Gly Pro Arg Gly Ala Gly
145                 150                 155                 160

Ile Ser Gly Arg Ser Gln Glu Gln Ser Val Lys Thr Val Pro Gly Ala
                165                 170                 175

Ser Asp Leu Phe Tyr Trp Pro Arg Arg Ala Gly Lys Leu Gln Gly Ser
            180                 185                 190

His His Lys Pro Leu Ser Lys Thr Ala Asn Gly Leu Ala Gly His Glu
        195                 200                 205

Gly Trp Thr Ile Ala Leu Pro Gly Arg Ala Leu Ala Gln Asn Gly Ser
    210                 215                 220
```

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Leu Gly Glu Gly Ile His Glu Pro Gly Gly Pro Arg Arg Gly Asn Ser
225                 230                 235                 240

Thr Asn Arg Arg Val Arg Leu Lys Asn Pro Phe Tyr Pro Leu Thr Gln
                245                 250                 255

Glu Ser Tyr Gly Ala Tyr Ala Val Met Cys Leu Ser Val Val Ile Phe
            260                 265                 270

Gly Thr Gly Ile Ile Gly Asn Leu Ala Val Met Cys Ile Val Cys His
        275                 280                 285

Asn Tyr Tyr Met Arg Ser Ile Ser Asn Ser Leu Leu Ala Asn Leu Ala
    290                 295                 300

Phe Trp Asp Phe Leu Ile Ile Phe Phe Cys Leu Pro Leu Val Ile Phe
305                 310                 315                 320

His Glu Leu Thr Lys Lys Trp Leu Leu Glu Asp Phe Ser Cys Lys Ile
                325                 330                 335

Val Pro Tyr Ile Glu Val Ala Ser Leu Gly Val Thr Thr Phe Thr Leu
            340                 345                 350

Cys Ala Leu Cys Ile Asp Arg Phe Arg Ala Ala Thr Asn Val Gln Met
        355                 360                 365

Tyr Tyr Glu Met Ile Glu Asn Cys Ser Ser Thr Thr Ala Lys Leu Ala
    370                 375                 380

Val Ile Trp Val Gly Ala Leu Leu Leu Ala Leu Pro Glu Val Val Leu
385                 390                 395                 400

Arg Gln Leu Ser Lys Glu Asp Leu Gly Phe Ser Gly Arg Ala Pro Ala
                405                 410                 415

Glu Arg Cys Ile Ile Lys Ile Ser Pro Asp Leu Pro Asp Thr Ile Tyr
            420                 425                 430

Val Leu Ala Leu Thr Tyr Asp Ser Ala Arg Leu Trp Trp Tyr Phe Gly
        435                 440                 445

Cys Tyr Phe Cys Leu Pro Thr Leu Phe Thr Ile Thr Cys Ser Leu Val
```

450 455 460

Thr Ala Arg Lys Ile Arg Lys Ala Glu Lys Ala Cys Thr Arg Gly Asn
465 470 475 480

Lys Arg Gln Ile Gln Leu Glu Ser Gln Met Asn Cys Thr Val Val Ala
485 490 495

Leu Thr Ile Leu Tyr Gly Phe Cys Ile Ile Pro Glu Asn Ile Cys Asn
500 505 510

Ile Val Thr Ala Tyr Met Ala Thr Gly Val Ser Gln Gln Thr Met Asp
515 520 525

Leu Leu Asn Ile Ile Ser Gln Phe Leu Leu Phe Phe Lys Ser Cys Val
530 535 540

Thr Pro Val Leu Leu Phe Cys Leu Cys Lys Pro Phe Ser Arg Ala Phe
545 550 555 560

Met Glu Cys Cys Cys Cys Cys Cys Glu Glu Cys Ile Gln Lys Ser Ser
565 570 575

Thr Val Thr Ser Asp Asp Asn Asp Asn Glu Tyr Thr Thr Glu Leu Glu
580 585 590

Leu Ser Pro Phe Ser Thr Ile Arg Arg Glu Met Ser Thr Phe Ala Ser
595 600 605

Val Gly Thr His Cys
610

<210> 11
<211> 1086
<212> DNA
<213> Homo sapiens

<400> 11
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gcggtggaga caaccgtgct ggtgctcatc tttgcagtgt cgctgctggg caacgtgtgc 180

gccctggtgc tggtggcgcg ccgacgacgc cgcggcgcga ctgcctgcct ggtactcaac 240

ctcttctgcg cggacctgct cttcatcagc gctatccctc tggtgctggc cgtgcgctgg 300

actgaggcct ggctgctggg ccccgttgcc tgccacctgc tcttctacgt gatgaccctg 360

agcggcagcg tcaccatcct cacgctggcc gcggtcagcc tggagcgcat ggtgtgcatc 420

gtgcacctgc agcgcggcgt gcggggtcct gggcggcggg cgcgggcagt gctgctggcg 480

ctcatctggg gctattcggc ggtcgccgct ctgcctctct gcgtcttctt tcgagtcgtc 540

ccgcaacggc tccccggcgc cgaccaggaa atttcgattt gcacactgat ttggcccacc 600

attcctggag agatctcgtg ggatgtctct tttgttactt tgaacttctt ggtgccagga 660

ctggtcattg tgatcagtta ctccaaaatt ttacagatca caaaggcatc aaggaagagg 720

ctcacggtaa gcctggccta ctcggagagc caccagatcc gcgtgtccca gcaggacttc 780

cggctcttcc gcaccctctt cctcctcatg gtctccttct tcatcatgtg gagccccatc 840

atcatcacca tcctcctcat cctgatccag aacttcaagc aagacctggt catctggccg 900

tccctcttct tctgggtggt ggccttcaca tttgctaatt cagccctaaa ccccatcctc 960

tacaacatga cactgtgcag gaatgagtgg aagaaaattt tttgctgctt ctggttccca 1020

gaaaagggag ccattttaac agacacatct gtcaaaagaa atgacttgtc gattatttct 1080

ggctaa 1086

<210> 12
<211> 361
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 12

Met Ser Pro Glu Cys Ala Arg Ala Ala Gly Asp Ala Pro Leu Arg Ser
1 5 10 15

Leu Glu Gln Ala Asn Arg Thr Arg Phe Pro Phe Phe Ser Asp Val Lys
20 25 30

Gly Asp His Arg Leu Val Leu Ala Ala Val Glu Thr Thr Val Leu Val
35 40 45

Leu Ile Phe Ala Val Ser Leu Leu Gly Asn Val Cys Ala Leu Val Leu
50 55 60

```
Val Ala Arg Arg Arg Arg Gly Ala Thr Ala Cys Leu Val Leu Asn
65                  70                  75                  80

Leu Phe Cys Ala Asp Leu Leu Phe Ile Ser Ala Ile Pro Leu Val Leu
                85                  90                  95

Ala Val Arg Trp Thr Glu Ala Trp Leu Leu Gly Pro Val Ala Cys His
            100                 105                 110

Leu Leu Phe Tyr Val Met Thr Leu Ser Gly Ser Val Thr Ile Leu Thr
        115                 120                 125

Leu Ala Ala Val Ser Leu Glu Arg Met Val Cys Ile Val His Leu Gln
    130                 135                 140

Arg Gly Val Arg Gly Pro Gly Arg Arg Ala Arg Ala Val Leu Leu Ala
145                 150                 155                 160

Leu Ile Trp Gly Tyr Ser Ala Val Ala Ala Leu Pro Leu Cys Val Phe
                165                 170                 175

Phe Arg Val Val Pro Gln Arg Leu Pro Gly Ala Asp Gln Glu Ile Ser
            180                 185                 190

Ile Cys Thr Leu Ile Trp Pro Thr Ile Pro Gly Glu Ile Ser Trp Asp
        195                 200                 205

Val Ser Phe Val Thr Leu Asn Phe Leu Val Pro Gly Leu Val Ile Val
    210                 215                 220

Ile Ser Tyr Ser Lys Ile Leu Gln Ile Thr Lys Ala Ser Arg Lys Arg
225                 230                 235                 240

Leu Thr Val Ser Leu Ala Tyr Ser Glu Ser His Gln Ile Arg Val Ser
                245                 250                 255

Gln Gln Asp Phe Arg Leu Phe Arg Thr Leu Phe Leu Leu Met Val Ser
            260                 265                 270

Phe Phe Ile Met Trp Ser Pro Ile Ile Ile Thr Ile Leu Leu Ile Leu
        275                 280                 285

Ile Gln Asn Phe Lys Gln Asp Leu Val Ile Trp Pro Ser Leu Phe Phe
```

290 295 300

Trp Val Val Ala Phe Thr Phe Ala Asn Ser Ala Leu Asn Pro Ile Leu
305 310 315 320

Tyr Asn Met Thr Leu Cys Arg Asn Glu Trp Lys Lys Ile Phe Cys Cys
325 330 335

Phe Trp Phe Pro Glu Lys Gly Ala Ile Leu Thr Asp Thr Ser Val Lys
340 345 350

Arg Asn Asp Leu Ser Ile Ile Ser Gly
355 360

<210> 13
<211> 1212
<212> DNA
<213> Homo sapiens

<400> 13
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tgtgccacat acctgctgat cttcgtggtg ggcgctgtgg gcaatgggct gacctgtctg 180

gtcatcctgc gccacaaggc catgcgcacg cctaccaact actacctctt cagcctggcc 240

gtgtcggacc tgctggtgct gctggtgggc ctgcccctgg agctctatga gatgtggcac 300

aactaccct tcctgctggg cgttggtggc tgctatttcc gcacgctact gtttgagatg 360

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gccgtctggg gtcttgccat gctctgctcc ctgcccaaca ccagcctgca cggcatccgg 540

cagctgcacg tgccctgccg gggcccagtg ccagactcag ctgtttgcat gctggtccgc 600

ccacgggccc tctacaacat ggtagtgcag accaccgcgc tgctcttctt ctgcctgccc 660

atggccatca tgagcgtgct ctacctgctc attgggctgc gactgcggcg ggagaggctg 720

ctgctcatgc aggaggccaa gggcaggggc tctgcagcag ccaggtccag atacacctgc 780

aggctccagc agcacgatcg gggccggaga caagtgacca agatgctgtt tgtcctggtc 840

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tcacagtgga cagatggcct gcacctggcc ttccagcacg tgcacgtcat ctccggcatc 960

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cacagctccc acagcctcag caggatgacc acaggcagca ccctgtgtga tgtgggctcc 1140

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gatccatcct ga 1212

<210> 14
<211> 403
<212> PRT
<213> Homo sapiens

<400> 14

Met Ala Cys Asn Gly Ser Ala Ala Arg Gly His Phe Asp Pro Glu Asp
1 5 10 15

Leu Asn Leu Thr Asp Glu Ala Leu Arg Leu Lys Tyr Leu Gly Pro Gln
20 25 30

Gln Thr Glu Leu Phe Met Pro Ile Cys Ala Thr Tyr Leu Leu Ile Phe
35 40 45

Val Val Gly Ala Val Gly Asn Gly Leu Thr Cys Leu Val Ile Leu Arg
50 55 60

His Lys Ala Met Arg Thr Pro Thr Asn Tyr Tyr Leu Phe Ser Leu Ala
65 70 75 80

Val Ser Asp Leu Leu Val Leu Leu Val Gly Leu Pro Leu Glu Leu Tyr
85 90 95

Glu Met Trp His Asn Tyr Pro Phe Leu Leu Gly Val Gly Gly Cys Tyr
100 105 110

Phe Arg Thr Leu Leu Phe Glu Met Val Cys Leu Ala Ser Val Leu Asn
115 120 125

Val Thr Ala Leu Ser Val Glu Arg Tyr Val Ala Val Val His Pro Leu
130 135 140

Gln Ala Arg Ser Met Val Thr Arg Ala His Val Arg Arg Val Leu Gly
145 150 155 160

```
Ala Val Trp Gly Leu Ala Met Leu Cys Ser Leu Pro Asn Thr Ser Leu
                165                 170                 175

His Gly Ile Arg Gln Leu His Val Pro Cys Arg Gly Pro Val Pro Asp
            180                 185                 190

Ser Ala Val Cys Met Leu Val Arg Pro Arg Ala Leu Tyr Asn Met Val
        195                 200                 205

Val Gln Thr Thr Ala Leu Leu Phe Phe Cys Leu Pro Met Ala Ile Met
    210                 215                 220

Ser Val Leu Tyr Leu Leu Ile Gly Leu Arg Leu Arg Arg Glu Arg Leu
225                 230                 235                 240

Leu Leu Met Gln Glu Ala Lys Gly Arg Gly Ser Ala Ala Ala Arg Ser
                245                 250                 255

Arg Tyr Thr Cys Arg Leu Gln Gln His Asp Arg Gly Arg Arg Gln Val
            260                 265                 270

Thr Lys Met Leu Phe Val Leu Val Val Val Phe Gly Ile Cys Trp Ala
        275                 280                 285

Pro Phe His Ala Asp Arg Val Met Trp Ser Val Val Ser Gln Trp Thr
    290                 295                 300

Asp Gly Leu His Leu Ala Phe Gln His Val His Val Ile Ser Gly Ile
305                 310                 315                 320

Phe Phe Tyr Leu Gly Ser Ala Ala Asn Pro Val Leu Tyr Ser Leu Met
                325                 330                 335

Ser Ser Arg Phe Arg Glu Thr Phe Gln Glu Ala Leu Cys Leu Gly Ala
            340                 345                 350

Cys Cys His Arg Leu Arg Pro Arg His Ser Ser His Ser Leu Ser Arg
        355                 360                 365

Met Thr Thr Gly Ser Thr Leu Cys Asp Val Gly Ser Leu Gly Ser Trp
    370                 375                 380
```

Val His Pro Leu Ala Gly Asn Asp Gly Pro Glu Ala Gln Gln Glu Thr
385 390 395 400

Asp Pro Ser

<210> 15
<211> 930
<212> DNA
<213> Homo sapiens

<400> 15
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ctgggcttct acgcctactt gggcgtcctg ctggtgctag gcctgctgct caacagcctg 120

gcgctctggg tgttctgctg ccgcatgcag cagtggacgg agacccgcat ctacatgacc 180

aacctggcgg tggccgacct ctgcctgctg tgcaccttgc ccttcgtgct gcactccctg 240

cgagacacct cagacacgcc gctgtgccag ctctcccagg gcatctacct gaccaacagg 300

tacatgagca tcagcctggt cacggccatc gccgtggacc gctatgtggc cgtgcggcac 360

ccgctgcgtg cccgcgggct gcggtccccc aggcaggctg cggccgtgtg cgcggtcctc 420

tgggtgctgg tcatcggctc cctggtggct cgctggctcc tggggattca ggagggcggc 480

ttctgcttca ggagcacccg gcacaatttc aactccatgc ggttcccgct gctgggattc 540

tacctgcccc tggccgtggt ggtcttctgc tccctgaagg tggtgactgc cctggcccag 600

aggccaccca ccgacgtggg gcaggcagag gccacccgca aggctgcccg catggtctgg 660

gccaacctcc tggtgttcgt ggtctgcttc ctgcccctgc acgtggggct gacagtgcgc 720

ctcgcagtgg gctggaacgc ctgtgccctc ctggagacga tccgtcgcgc cctgtacata 780

accagcaagc tctcagatgc caactgctgc ctggacgcca tctgctacta ctacatggcc 840

aaggagttcc aggaggcgtc tgcactggcc gtggctcccc gtgctaaggc ccacaaaagc 900

caggactctc tgtgcgtgac cctcgcctaa 930

<210> 16
<211> 309
<212> PRT
<213> Homo sapiens

<400> 16

Met Asn Gly Thr Tyr Asn Thr Cys Gly Ser Ser Asp Leu Thr Trp Pro
1 5 10 15

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Pro Ala Ile Lys Leu Gly Phe Tyr Ala Tyr Leu Gly Val Leu Leu Val
            20                  25                  30

Leu Gly Leu Leu Leu Asn Ser Leu Ala Leu Trp Val Phe Cys Cys Arg
        35                  40                  45

Met Gln Gln Trp Thr Glu Thr Arg Ile Tyr Met Thr Asn Leu Ala Val
    50                  55                  60

Ala Asp Leu Cys Leu Leu Cys Thr Leu Pro Phe Val Leu His Ser Leu
65                  70                  75                  80

Arg Asp Thr Ser Asp Thr Pro Leu Cys Gln Leu Ser Gln Gly Ile Tyr
                85                  90                  95

Leu Thr Asn Arg Tyr Met Ser Ile Ser Leu Val Thr Ala Ile Ala Val
            100                 105                 110

Asp Arg Tyr Val Ala Val Arg His Pro Leu Arg Ala Arg Gly Leu Arg
        115                 120                 125

Ser Pro Arg Gln Ala Ala Ala Val Cys Ala Val Leu Trp Val Leu Val
    130                 135                 140

Ile Gly Ser Leu Val Ala Arg Trp Leu Leu Gly Ile Gln Glu Gly Gly
145                 150                 155                 160

Phe Cys Phe Arg Ser Thr Arg His Asn Phe Asn Ser Met Arg Phe Pro
                165                 170                 175

Leu Leu Gly Phe Tyr Leu Pro Leu Ala Val Val Val Phe Cys Ser Leu
            180                 185                 190

Lys Val Val Thr Ala Leu Ala Gln Arg Pro Pro Thr Asp Val Gly Gln
        195                 200                 205

Ala Glu Ala Thr Arg Lys Ala Ala Arg Met Val Trp Ala Asn Leu Leu
    210                 215                 220

Val Phe Val Val Cys Phe Leu Pro Leu His Val Gly Leu Thr Val Arg
225                 230                 235                 240
```

Leu Ala Val Gly Trp Asn Ala Cys Ala Leu Leu Glu Thr Ile Arg Arg
245 250 255

Ala Leu Tyr Ile Thr Ser Lys Leu Ser Asp Ala Asn Cys Cys Leu Asp
260 265 270

Ala Ile Cys Tyr Tyr Tyr Met Ala Lys Glu Phe Gln Glu Ala Ser Ala
275 280 285

Leu Ala Val Ala Pro Arg Ala Lys Ala His Lys Ser Gln Asp Ser Leu
290 295 300

Cys Val Thr Leu Ala
305

<210> 17
<211> 1446
<212> DNA
<213> Homo sapiens

<400> 17
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agggtctctg ggggtgcccc cctgcacctg ggcaggcaca gagccgagac ccaggagcag 120

cagagccgat ccaagagggg caccgaggat gaggaggcca agggcgtgca gcagtatgtg 180

cctgaggagt gggcggagta cccccggccc attcaccctg ctggcctgca gccaaccaag 240

cccttggtgg ccaccagccc taaccccgac aaggatgggg gcaccccaga cagtgggcag 300

gaactgaggg gcaatctgac aggggcacca gggcagaggc tacagatcca gaacccccctg 360

tatccggtga ccgagagctc ctacagtgcc tatgccatca tgcttctggc gctggtggtg 420

tttgcggtgg gcattgtggg caacctgtcg gtcatgtgca tcgtgtggca cagctactac 480

ctgaagagcg cctggaactc catccttgcc agcctggccc tctgggattt tctggtcctc 540

tttttctgcc tccctattgt catcttcaac gagatcacca agcagaggct actgggtgac 600

gtttcttgtc gtgccgtgcc cttcatggag gtctcctctc tgggagtcac gactttcagc 660

ctctgtgccc tgggcattga ccgcttccac gtggccacca gcaccctgcc caaggtgagg 720

cccatcgagc ggtgccaatc catcctggcc aagttggctg tcatctgggt gggctccatg 780

acgctggctg tgcctgagct cctgctgtgg cagctggcac aggagcctgc ccccaccatg 840

ggcaccctgg actcatgcat catgaaaccc tcagccagcc tgcccgagtc cctgtattca 900

ctggtgatga cctaccagaa cgcccgcatg tggtggtact ttggctgcta cttctgcctg 960

cccatcctct tcacagtcac ctgccagctg gtgacatggc gggtgcgagg ccctccaggg 1020

aggaagtcag agtgcagggc cagcaagcac gagcagtgtg agagccagct caacagcacc 1080

gtggtgggcc tgaccgtggt ctacgccttc tgcaccctcc cagagaacgt ctgcaacatc 1140

gtggtggcct acctctccac cgagctgacc cgccagaccc tggacctcct gggcctcatc 1200

aaccagttct ccaccttctt caagggcgcc atcaccccag tgctgctcct ttgcatctgc 1260

aggccgctgg gccaggcctt cctggactgc tgctgctgct gctgctgtga ggagtgcggc 1320

ggggcttcgg aggcctctgc tgccaatggg tcggacaaca agctcaagac cgaggtgtcc 1380

tcttccatct acttccacaa gcccagggag tcacccccac tcctgccct gggcacacct 1440

tgctga 1446

<210> 18
<211> 481
<212> PRT
<213> Homo sapiens

<400> 18

Met Arg Trp Leu Trp Pro Leu Ala Val Ser Leu Ala Val Ile Leu Ala
1 5 10 15

Val Gly Leu Ser Arg Val Ser Gly Gly Ala Pro Leu His Leu Gly Arg
20 25 30

His Arg Ala Glu Thr Gln Glu Gln Gln Ser Arg Ser Lys Arg Gly Thr
35 40 45

Glu Asp Glu Glu Ala Lys Gly Val Gln Gln Tyr Val Pro Glu Glu Trp
50 55 60

Ala Glu Tyr Pro Arg Pro Ile His Pro Ala Gly Leu Gln Pro Thr Lys
65 70 75 80

Pro Leu Val Ala Thr Ser Pro Asn Pro Asp Lys Asp Gly Gly Thr Pro
85 90 95

Asp Ser Gly Gln Glu Leu Arg Gly Asn Leu Thr Gly Ala Pro Gly Gln
100 105 110

Arg Leu Gln Ile Gln Asn Pro Leu Tyr Pro Val Thr Glu Ser Ser Tyr
115 120 125

```
Ser Ala Tyr Ala Ile Met Leu Leu Ala Leu Val Val Phe Ala Val Gly
    130                 135                 140

Ile Val Gly Asn Leu Ser Val Met Cys Ile Val Trp His Ser Tyr Tyr
145                 150                 155                 160

Leu Lys Ser Ala Trp Asn Ser Ile Leu Ala Ser Leu Ala Leu Trp Asp
                165                 170                 175

Phe Leu Val Leu Phe Phe Cys Leu Pro Ile Val Ile Phe Asn Glu Ile
            180                 185                 190

Thr Lys Gln Arg Leu Leu Gly Asp Val Ser Cys Arg Ala Val Pro Phe
        195                 200                 205

Met Glu Val Ser Ser Leu Gly Val Thr Thr Phe Ser Leu Cys Ala Leu
    210                 215                 220

Gly Ile Asp Arg Phe His Val Ala Thr Ser Thr Leu Pro Lys Val Arg
225                 230                 235                 240

Pro Ile Glu Arg Cys Gln Ser Ile Leu Ala Lys Leu Ala Val Ile Trp
                245                 250                 255

Val Gly Ser Met Thr Leu Ala Val Pro Glu Leu Leu Leu Trp Gln Leu
            260                 265                 270

Ala Gln Glu Pro Ala Pro Thr Met Gly Thr Leu Asp Ser Cys Ile Met
        275                 280                 285

Lys Pro Ser Ala Ser Leu Pro Glu Ser Leu Tyr Ser Leu Val Met Thr
    290                 295                 300

Tyr Gln Asn Ala Arg Met Trp Trp Tyr Phe Gly Cys Tyr Phe Cys Leu
305                 310                 315                 320

Pro Ile Leu Phe Thr Val Thr Cys Gln Leu Val Thr Trp Arg Val Arg
                325                 330                 335

Gly Pro Pro Gly Arg Lys Ser Glu Cys Arg Ala Ser Lys His Glu Gln
            340                 345                 350
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Cys Glu Ser Gln Leu Asn Ser Thr Val Val Gly Leu Thr Val Val Tyr
355 360 365

Ala Phe Cys Thr Leu Pro Glu Asn Val Cys Asn Ile Val Val Ala Tyr
370 375 380

Leu Ser Thr Glu Leu Thr Arg Gln Thr Leu Asp Leu Leu Gly Leu Ile
385 390 395 400

Asn Gln Phe Ser Thr Phe Phe Lys Gly Ala Ile Thr Pro Val Leu Leu
405 410 415

Leu Cys Ile Cys Arg Pro Leu Gly Gln Ala Phe Leu Asp Cys Cys Cys
420 425 430

Cys Cys Cys Cys Glu Glu Cys Gly Gly Ala Ser Glu Ala Ser Ala Ala
435 440 445

Asn Gly Ser Asp Asn Lys Leu Lys Thr Glu Val Ser Ser Ser Ile Tyr
450 455 460

Phe His Lys Pro Arg Glu Ser Pro Pro Leu Leu Pro Leu Gly Thr Pro
465 470 475 480

Cys

<210> 19
<211> 29
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 19
aaagattcag gtgtgggaag atggaaacc 29

<210> 20
<211> 29
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

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aaaggatccc cgacctcaca ttgcttgta 29

<210> 21
<211> 30
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 21
caggaattca tcagaacaga caccatggca 30

<210> 22
<211> 31
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 22
gcaggatcca gagcagtttt ttcgaaaccc t 31

<210> 23
<211> 33
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 23
tccaagcttc aagggtctct ccacgatggc ctg 33

<210> 24
<211> 33
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 24
tgcgaattct ctgtggcccc ctgacccccc aaa 33

<210> 25
<211> 36
<212> DNA
<213> Unknown

<220>
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<400> 25
ggtaagctta ccatggcctg caacagcacg tccctt 36

<210> 26
<211> 33
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 26
gacgaattca accgcagact ggttttcatt gca 33

<210> 27
<211> 33
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 27
gcaagcttgt gccctcacca agccatgcga gcc 33

<210> 28
<211> 30
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 28
cggaattcag caatgagttc cgacagaagc 30

<210> 29
<211> 37
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 29
accatggctt gcaatggcag tgcggccagg gggcact 37

<210> 30
<211> 39

<212> DNA
<213> Unknown

<220>
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<400> 30
cgaccaggac aaacagcatc ttggtcactt gtctccggc 39

<210> 31
<211> 39
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 31
gaccaagatg ctgtttgtcc tggtcgtggt gtttggcat 39

<210> 32
<211> 35
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 32
cggaattcag gatggatcgg tctcttgctg cgcct 35

<210> 33
<211> 30
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 33
gcgaattccg gctccctgtg ctgccccagg 30

<210> 34
<211> 30
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 34
gcggatcccg gagcccccga gacctggccc 30

<210> 35
<211> 31
<212> DNA
<213> Unknown

<220>
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<400> 35
ctggaattct cctgctcatc cagccatgcg g 31

<210> 36
<211> 30
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 36
cctggatccc cacccctact ggggcctcag 30

<210> 37
<211> 29
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 37
tccagccgtc ccaaacgtgt cttcgctgc 29

<210> 38
<211> 31
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 38
ctccttcggt cctcctatcg ttgtcagaag t 31

<210> 39
<211> 33
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 39
cagaagcaca gatcaaaaaa gatcatcttc ctg 33

<210> 40
<211> 31
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 40
acaggaatca cagccgaggg ggagtgccac t 31

<210> 41
<211> 32
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 41
tgtgttcttt ccggcatgtt ttcttgggct tg 32

<210> 42
<211> 32
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 42
caagcccaag aaaacatgcc ggaaagaaca ca 32

<210> 43
<211> 33
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 43
ctcatggtca catgttgtgt gtatgccatc aag 33

<210> 44
<211> 33
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 44
cttgatggca tacacacaac atgtgaccat gag 33

<210> 45
<211> 34
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 45
acgaagccaa gcccaaggga ttcactatgt acac 34

<210> 46
<211> 34
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 46
gtgtacatag tgaatccctt gggcttggct ccgt 34

<210> 47
<211> 35
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 47
gtcaccacct ttcacccgat gtgctctgtg catag 35

<210> 48
<211> 35
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 48
ctatgcacag agcacatcgg gtgaaaggtg gtgac 35

<210> 49
<211> 36

<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 49
cctttgttc tttaagtcct atgtcacccc agtcct 36

<210> 50
<211> 36
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 50
aggactgggg tgacatagga cttaaagaac aaaagg 36

<210> 51
<211> 31
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 51
atgtggagcc ccatcttcat caccatcctc c 31

<210> 52
<211> 31
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 52
ggaggatggt gatgaagatg gggctccaca t 31

<210> 53
<211> 33
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 53
gccgcggtca gcctgaatcg catggtgtgc atc 33

<210> 54
<211> 33
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 54
gatgcacacc atgcgattca ggctgaccgc ggc 33

<210> 55
<211> 29
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 55
ggccggagac aagtgaaaag atgctgttt 29

<210> 56
<211> 30
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 56
aaacagcatc tttttcactt gtctccggcc 30

<210> 57
<211> 27
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 57
gagagccagc tcaagagcac cgtggtg 27

<210> 58
<211> 31
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 58
ctccttcggt cctcctatcg ttgtcagaag t 31

<210> 59
<211> 31
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 59
agtggcactc cccctcggct gtgattcctg t 31

<210> 60
<211> 30
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 60
gccacccgca aggctaaacg catggtctgg 30

<210> 61
<211> 31
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 61
ctccttcggt cctcctatcg ttgtcagaag t 31

<210> 62
<211> 1062
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 62
atggaaacca acttctccat tcctctgaat gaaactgagg aggtgctccc tgagcctgct 60

ggccacaccg ttctgtggat cttctcattg ctagtccacg gagtcacctt tgtcttcggg 120

gtcctgggca atgggcttgt gatctgggtg gctggattcc ggatgacacg cacagtcaac 180

accatctgtt acctgaacct ggccctagct gacttctctt tcagtgccat cctaccattc 240

cgaatggtct cagtcgccat gagagaaaaa tggccttttg gctcattcct atgtaagtta 300

gttcatgtta tgatagacat caacctgttt gtcagtgtct acctgatcac catcattgct 360

ctggaccgct gtatttgtgt cctgcatcca gcctgggccc agaaccatcg caccatgagt 420

ctggccaaga gggtgatgac gggactctgg attttcacca tagtccttac cttaccaaat 480

ttcatcttct ggactacaat aagtactacg aatggggaca catactgtat tttcaacttt 540

gcattctggg gtgacactgc tgtagagagg ttgaacgtgt tcattaccat ggccaaggtc 600

tttctgatcc tccacttcat tattggcttc agcgtgccta tgtccatcat cacagtctgc 660

tatgggatca tcgctgccaa aattcacaga aaccacatga ttaaatccag ccgtcccaaa 720

cgtgtcttcg ctgctgtggt ggcttctttc ttcatctgtt ggttccctta tgaactaatt 780

ggcattctaa tggcagtctg gctcaaagag atgttgttaa atggcaaata caaaatcatt 840

cttgtcctga ttaacccaac aagctccttg gccttttta acagctgcct caacccaatt 900

ctctacgtct ttatgggtcg taacttccaa gaaagactga ttcgctcttt gcccactagt 960

ttggagaggg ccctgactga ggtccctgac tcagcccaga ccagcaacac agacaccact 1020

tctgcttcac ctcctgagga gacggagtta caagcaatgt ga 1062

<210> 63
<211> 353
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 63

Met Glu Thr Asn Phe Ser Ile Pro Leu Asn Glu Thr Glu Glu Val Leu
1 5 10 15

Pro Glu Pro Ala Gly His Thr Val Leu Trp Ile Phe Ser Leu Leu Val
20 25 30

His Gly Val Thr Phe Val Phe Gly Val Leu Gly Asn Gly Leu Val Ile
35 40 45

Trp Val Ala Gly Phe Arg Met Thr Arg Thr Val Asn Thr Ile Cys Tyr
50 55 60

Leu Asn Leu Ala Leu Ala Asp Phe Ser Phe Ser Ala Ile Leu Pro Phe
65 70 75 80

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Arg Met Val Ser Val Ala Met Arg Glu Lys Trp Pro Phe Gly Ser Phe
                85                  90                  95

Leu Cys Lys Leu Val His Val Met Ile Asp Ile Asn Leu Phe Val Ser
            100                 105                 110

Val Tyr Leu Ile Thr Ile Ile Ala Leu Asp Arg Cys Ile Cys Val Leu
        115                 120                 125

His Pro Ala Trp Ala Gln Asn His Arg Thr Met Ser Leu Ala Lys Arg
    130                 135                 140

Val Met Thr Gly Leu Trp Ile Phe Thr Ile Val Leu Thr Leu Pro Asn
145                 150                 155                 160

Phe Ile Phe Trp Thr Thr Ile Ser Thr Thr Asn Gly Asp Thr Tyr Cys
                165                 170                 175

Ile Phe Asn Phe Ala Phe Trp Gly Asp Thr Ala Val Glu Arg Leu Asn
            180                 185                 190

Val Phe Ile Thr Met Ala Lys Val Phe Leu Ile Leu His Phe Ile Ile
        195                 200                 205

Gly Phe Ser Val Pro Met Ser Ile Ile Thr Val Cys Tyr Gly Ile Ile
    210                 215                 220

Ala Ala Lys Ile His Arg Asn His Met Ile Lys Ser Ser Arg Pro Lys
225                 230                 235                 240

Arg Val Phe Ala Ala Val Val Ala Ser Phe Phe Ile Cys Trp Phe Pro
                245                 250                 255

Tyr Glu Leu Ile Gly Ile Leu Met Ala Val Trp Leu Lys Glu Met Leu
            260                 265                 270

Leu Asn Gly Lys Tyr Lys Ile Ile Leu Val Leu Ile Asn Pro Thr Ser
        275                 280                 285

Ser Leu Ala Phe Phe Asn Ser Cys Leu Asn Pro Ile Leu Tyr Val Phe
    290                 295                 300
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Met Gly Arg Asn Phe Gln Glu Arg Leu Ile Arg Ser Leu Pro Thr Ser
305 310 315 320

Leu Glu Arg Ala Leu Thr Glu Val Pro Asp Ser Ala Gln Thr Ser Asn
325 330 335

Thr Asp Thr Thr Ser Ala Ser Pro Pro Glu Glu Thr Glu Leu Gln Ala
340 345 350

Met

<210> 64
<211> 1029
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 64
atggcagagc atgattacca tgaagactat gggttcagca gtttcaatga cagcagccag 60

gaggagcatc aagccttcct gcagttcagc aaggtctttc tgccctgcat gtacctggtg 120

gtgtttgtct gtggtctggt ggggaactct ctggtgctgg tcatatccat cttctaccat 180

aagttgcaga gcctgacgga tgtgttcctg gtgaacctac ccctggctga cctggtgttt 240

gtctgcactc tgcccttctg ggcctatgca ggcatccatg aatgggtgtt tggccaggtc 300

atgtgcaaaa gcctactggg catctacact attaacttct acacgtccat gctcatcctc 360

acctgcatca ctgtggatcg tttcattgta gtggttaagg ccaccaaggc ctacaaccag 420

caagccaaga ggatgacctg gggcaaggtc accagcttgc tcatctgggt gatatccctg 480

ctggtttcct tgccccaaat tatctatggc aatgtcttta atctcgacaa gctcatatgt 540

ggttaccatg acgaggcaat ttccactgtg gttcttgcca cccagatgac actggggttc 600

ttcttgccac tgctcaccat gattgtctgc tattcagtca taatcaaaac actgcttcat 660

gctggaggct tccagaagca cagatcaaaa aagatcatct tcctggtgat ggctgtgttc 720

ctgctgaccc agatgccctt caacctcatg aagttcatcc gcagcacaca ctgggaatac 780

tatgccatga ccagctttca ctacaccatc atggtgacag aggccatcgc atacctgagg 840

gcctgcctta accctgtgct ctatgccttt gtcagcctga agtttcgaaa gaacttctgg 900

aaacttgtga aggacattgg ttgcctccct taccttgggg tctcacatca atggaaatct 960

tctgaggaca attccaagac tttttctgcc tcccacaatg tggaggccac cagcatgttc 1020

cagttatag 1029

<210> 65
<211> 342
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 65

Met Ala Glu His Asp Tyr His Glu Asp Tyr Gly Phe Ser Ser Phe Asn
1 5 10 15

Asp Ser Ser Gln Glu Glu His Gln Ala Phe Leu Gln Phe Ser Lys Val
20 25 30

Phe Leu Pro Cys Met Tyr Leu Val Val Phe Val Cys Gly Leu Val Gly
35 40 45

Asn Ser Leu Val Leu Val Ile Ser Ile Phe Tyr His Lys Leu Gln Ser
50 55 60

Leu Thr Asp Val Phe Leu Val Asn Leu Pro Leu Ala Asp Leu Val Phe
65 70 75 80

Val Cys Thr Leu Pro Phe Trp Ala Tyr Ala Gly Ile His Glu Trp Val
85 90 95

Phe Gly Gln Val Met Cys Lys Ser Leu Leu Gly Ile Tyr Thr Ile Asn
100 105 110

Phe Tyr Thr Ser Met Leu Ile Leu Thr Cys Ile Thr Val Asp Arg Phe
115 120 125

Ile Val Val Val Lys Ala Thr Lys Ala Tyr Asn Gln Gln Ala Lys Arg
130 135 140

Met Thr Trp Gly Lys Val Thr Ser Leu Leu Ile Trp Val Ile Ser Leu
145 150 155 160

Leu Val Ser Leu Pro Gln Ile Ile Tyr Gly Asn Val Phe Asn Leu Asp

165 170 175

Lys Leu Ile Cys Gly Tyr His Asp Glu Ala Ile Ser Thr Val Val Leu
180 185 190

Ala Thr Gln Met Thr Leu Gly Phe Phe Leu Pro Leu Leu Thr Met Ile
195 200 205

Val Cys Tyr Ser Val Ile Ile Lys Thr Leu Leu His Ala Gly Gly Phe
210 215 220

Gln Lys His Arg Ser Lys Lys Ile Ile Phe Leu Val Met Ala Val Phe
225 230 235 240

Leu Leu Thr Gln Met Pro Phe Asn Leu Met Lys Phe Ile Arg Ser Thr
245 250 255

His Trp Glu Tyr Tyr Ala Met Thr Ser Phe His Tyr Thr Ile Met Val
260 265 270

Thr Glu Ala Ile Ala Tyr Leu Arg Ala Cys Leu Asn Pro Val Leu Tyr
275 280 285

Ala Phe Val Ser Leu Lys Phe Arg Lys Asn Phe Trp Lys Leu Val Lys
290 295 300

Asp Ile Gly Cys Leu Pro Tyr Leu Gly Val Ser His Gln Trp Lys Ser
305 310 315 320

Ser Glu Asp Asn Ser Lys Thr Phe Ser Ala Ser His Asn Val Glu Ala
325 330 335

Thr Ser Met Phe Gln Leu
340

<210> 66
<211> 2748
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 66
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ctggaggtgc tcctgtgcgc gctggcggcg gcggcgcgcg gccaggagat gtacgccccg 120

cactcaatcc ggatcgaggg ggacgtcacc ctcgggggggc tgttccccgt gcacgccaag 180

ggtcccagcg gagtgccctg cggcgacatc aagagggaaa acgggatcca caggctggaa 240

gcgatgctct acgccctgga ccagatcaac agtgatccca acctactgcc caacgtgacg 300

ctgggcgcgc ggatcctgga cacttgttcc agggacactt acgcgctcga acagtcgctt 360

actttcgtcc aggcgctcat ccagaaggac acctccgacg tgcgctgcac caacggcgaa 420

ccgccggttt tcgtcaagcc ggagaaagta gttggagtga ttggggcttc ggggagttcg 480

gtctccatca tggtagccaa catcctgagg ctcttccaga tcccccagat tagttatgca 540

tcaacggcac ccgagctaag tgatgaccgg cgctatgact tcttctctcg cgtggtgcca 600

cccgattcct tccaagccca ggccatggta gacattgtaa aggccctagg ctggaattat 660

gtgtctaccc tcgcatcgga aggaagttat ggagagaaag gtgtggagtc cttcacgcag 720

atttccaaag aggcaggtgg actctgcatt gcccagtccg tgagaatccc ccaggaacgc 780

aaagacagga ccattgactt tgatagaatt atcaaacagc tcctggacac ccccaactcc 840

agggccgtcg tgatttttgc caacgatgag gatataaagc agatccttgc agcagccaaa 900

agagctgacc aagttggcca ttttctttgg gtgggatcag acagctgggg atccaaaata 960

aacccactgc accagcatga agatatcgca gaaggggcca tcaccattca gcccaagcga 1020

gccacggtgg aagggtttga tgcctacttt acgtcccgta cacttgaaaa caacagaaga 1080

aatgtatggt ttgccgaata ctgggaggaa aacttcaact gcaagttgac gattagtggg 1140

tcaaaaaaag aagacacaga tcgcaaatgc acaggacagg agagaattgg aaaagattcc 1200

aactatgagc aggagggtaa agtccagttc gtgattgacg cagtctatgc tatggctcac 1260

gcccttcacc acatgaacaa ggatctctgt gctgactacc ggggtgtctg cccagagatg 1320

gagcaagctg gaggcaagaa gttgctgaag tatatacgca atgttaattt caatggtagt 1380

gctggcactc cagtgatgtt taacaagaac ggggatgcac ctgggcgtta tgacatcttt 1440

cagtaccaga ccacaaacac cagcaacccg ggttaccgtc tgatcgggca gtggacagac 1500

gaacttcagc tcaatataga agacatgcag tggggtaaag gagtccgaga gatacccgcc 1560

tcagtgtgca cactaccatg taagccagga cagagaaaga agacacagaa aggaactcct 1620

tgctgttgga cctgtgagcc ttgcgatggt taccagtacc agtttgatga gatgacatgc 1680

cagcattgcc cctatgacca gaggcccaat gaaaatcgaa ccggatgcca ggatattccc 1740

atcatcaaac tggagtggca ctccccctcg gctgtgattc ctgtcttcct ggcaatgttg 1800

gggatcattg ccaccatctt tgtcatggcc actttcatcc gctacaatga cacgcccatt 1860

gtccgggcat ctgggcggga actcagctat gttcttttga cgggcatctt tctttgctac 1920

atcatcactt tcctgatgat tgccaaacca gatgtggcag tgtgttcttt ccggcgagtt 1980

ttcttgggct tgggtatgtg catcagttat gcagccctct tgacgaaaac aaatcggatt 2040

tatcgcatat ttgagcaggg caagaaatca gtaacagctc ccagactcat aagcccaaca 2100

tcacaactgg caatcacttc cagtttaata tcagttcagc ttctaggggt gttcatttgg 2160

tttggtgttg atccacccaa catcatcata gactacgatg aacacaagac aatgaaccct 2220

gagcaagcca gaggggttct caagtgtgac attacagatc tccaaatcat ttgctccttg 2280

ggatatagca ttcttctcat ggtcacatgt actgtgtatg ccatcaagac tcggggtgta 2340

cccgagaatt ttaacgaagc caagcccatt ggattcacta tgtacacgac atgtatagta 2400

tggcttgcct tcattccaat ttttttggc accgctcaat cagcggaaaa gctctacata 2460

caaactacca cgcttacaat ctccatgaac ctaagtgcat cagtggcgct ggggatgcta 2520

tacatgccga aagtgtacat catcattttc caccctgaac tcaatgtcca gaaacggaag 2580

cgaagcttca aggcggtagt cacagcagcc accatgtcat cgaggctgtc acacaaaccc 2640

agtgacagac ccaacggtga ggcaaagacc gagctctgtg aaaacgtaga cccaaacagc 2700

cctgctgcaa aaaagaagta tgtcagttat aataacctgg ttatctaa 2748

<210> 67
<211> 915
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 67

Met Val Gln Leu Arg Lys Leu Leu Arg Val Leu Thr Leu Met Lys Phe
1 5 10 15

Pro Cys Cys Val Leu Glu Val Leu Leu Cys Ala Leu Ala Ala Ala Ala
20 25 30

Arg Gly Gln Glu Met Tyr Ala Pro His Ser Ile Arg Ile Glu Gly Asp
35 40 45

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Val Thr Leu Gly Gly Leu Phe Pro Val His Ala Lys Gly Pro Ser Gly
    50                  55                  60

Val Pro Cys Gly Asp Ile Lys Arg Glu Asn Gly Ile His Arg Leu Glu
65                  70                  75                  80

Ala Met Leu Tyr Ala Leu Asp Gln Ile Asn Ser Asp Pro Asn Leu Leu
                85                  90                  95

Pro Asn Val Thr Leu Gly Ala Arg Ile Leu Asp Thr Cys Ser Arg Asp
            100                 105                 110

Thr Tyr Ala Leu Glu Gln Ser Leu Thr Phe Val Gln Ala Leu Ile Gln
        115                 120                 125

Lys Asp Thr Ser Asp Val Arg Cys Thr Asn Gly Glu Pro Pro Val Phe
    130                 135                 140

Val Lys Pro Glu Lys Val Val Gly Val Ile Gly Ala Ser Gly Ser Ser
145                 150                 155                 160

Val Ser Ile Met Val Ala Asn Ile Leu Arg Leu Phe Gln Ile Pro Gln
                165                 170                 175

Ile Ser Tyr Ala Ser Thr Ala Pro Glu Leu Ser Asp Asp Arg Arg Tyr
            180                 185                 190

Asp Phe Phe Ser Arg Val Val Pro Pro Asp Ser Phe Gln Ala Gln Ala
        195                 200                 205

Met Val Asp Ile Val Lys Ala Leu Gly Trp Asn Tyr Val Ser Thr Leu
    210                 215                 220

Ala Ser Glu Gly Ser Tyr Gly Glu Lys Gly Val Glu Ser Phe Thr Gln
225                 230                 235                 240

Ile Ser Lys Glu Ala Gly Gly Leu Cys Ile Ala Gln Ser Val Arg Ile
                245                 250                 255

Pro Gln Glu Arg Lys Asp Arg Thr Ile Asp Phe Asp Arg Ile Ile Lys
            260                 265                 270

Gln Leu Leu Asp Thr Pro Asn Ser Arg Ala Val Val Ile Phe Ala Asn
```

275 280 285

Asp Glu Asp Ile Lys Gln Ile Leu Ala Ala Ala Lys Arg Ala Asp Gln
290 295 300

Val Gly His Phe Leu Trp Val Gly Ser Asp Ser Trp Gly Ser Lys Ile
305 310 315 320

Asn Pro Leu His Gln His Glu Asp Ile Ala Glu Gly Ala Ile Thr Ile
325 330 335

Gln Pro Lys Arg Ala Thr Val Glu Gly Phe Asp Ala Tyr Phe Thr Ser
340 345 350

Arg Thr Leu Glu Asn Asn Arg Arg Asn Val Trp Phe Ala Glu Tyr Trp
355 360 365

Glu Glu Asn Phe Asn Cys Lys Leu Thr Ile Ser Gly Ser Lys Lys Glu
370 375 380

Asp Thr Asp Arg Lys Cys Thr Gly Gln Glu Arg Ile Gly Lys Asp Ser
385 390 395 400

Asn Tyr Glu Gln Glu Gly Lys Val Gln Phe Val Ile Asp Ala Val Tyr
405 410 415

Ala Met Ala His Ala Leu His His Met Asn Lys Asp Leu Cys Ala Asp
420 425 430

Tyr Arg Gly Val Cys Pro Glu Met Glu Gln Ala Gly Gly Lys Lys Leu
435 440 445

Leu Lys Tyr Ile Arg Asn Val Asn Phe Asn Gly Ser Ala Gly Thr Pro
450 455 460

Val Met Phe Asn Lys Asn Gly Asp Ala Pro Gly Arg Tyr Asp Ile Phe
465 470 475 480

Gln Tyr Gln Thr Thr Asn Thr Ser Asn Pro Gly Tyr Arg Leu Ile Gly
485 490 495

Gln Trp Thr Asp Glu Leu Gln Leu Asn Ile Glu Asp Met Gln Trp Gly
500 505 510

```
Lys Gly Val Arg Glu Ile Pro Ala Ser Val Cys Thr Leu Pro Cys Lys
        515                 520                 525

Pro Gly Gln Arg Lys Lys Thr Gln Lys Gly Thr Pro Cys Cys Trp Thr
    530                 535                 540

Cys Glu Pro Cys Asp Gly Tyr Gln Tyr Gln Phe Asp Glu Met Thr Cys
545                 550                 555                 560

Gln His Cys Pro Tyr Asp Gln Arg Pro Asn Glu Asn Arg Thr Gly Cys
                565                 570                 575

Gln Asp Ile Pro Ile Ile Lys Leu Glu Trp His Ser Pro Ser Ala Val
            580                 585                 590

Ile Pro Val Phe Leu Ala Met Leu Gly Ile Ile Ala Thr Ile Phe Val
        595                 600                 605

Met Ala Thr Phe Ile Arg Tyr Asn Asp Thr Pro Ile Val Arg Ala Ser
    610                 615                 620

Gly Arg Glu Leu Ser Tyr Val Leu Leu Thr Gly Ile Phe Leu Cys Tyr
625                 630                 635                 640

Ile Ile Thr Phe Leu Met Ile Ala Lys Pro Asp Val Ala Val Cys Ser
                645                 650                 655

Phe Arg Arg Val Phe Leu Gly Leu Gly Met Cys Ile Ser Tyr Ala Ala
            660                 665                 670

Leu Leu Thr Lys Thr Asn Arg Ile Tyr Arg Ile Phe Glu Gln Gly Lys
        675                 680                 685

Lys Ser Val Thr Ala Pro Arg Leu Ile Ser Pro Thr Ser Gln Leu Ala
    690                 695                 700

Ile Thr Ser Ser Leu Ile Ser Val Gln Leu Leu Gly Val Phe Ile Trp
705                 710                 715                 720

Phe Gly Val Asp Pro Pro Asn Ile Ile Ile Asp Tyr Asp Glu His Lys
                725                 730                 735
```

Thr Met Asn Pro Glu Gln Ala Arg Gly Val Leu Lys Cys Asp Ile Thr
740 745 750

Asp Leu Gln Ile Ile Cys Ser Leu Gly Tyr Ser Ile Leu Leu Met Val
755 760 765

Thr Cys Thr Val Tyr Ala Ile Lys Thr Arg Gly Val Pro Glu Asn Phe
770 775 780

Asn Glu Ala Lys Pro Ile Gly Phe Thr Met Tyr Thr Thr Cys Ile Val
785 790 795 800

Trp Leu Ala Phe Ile Pro Ile Phe Phe Gly Thr Ala Gln Ser Ala Glu
805 810 815

Lys Leu Tyr Ile Gln Thr Thr Thr Leu Thr Ile Ser Met Asn Leu Ser
820 825 830

Ala Ser Val Ala Leu Gly Met Leu Tyr Met Pro Lys Val Tyr Ile Ile
835 840 845

Ile Phe His Pro Glu Leu Asn Val Gln Lys Arg Lys Arg Ser Phe Lys
850 855 860

Ala Val Val Thr Ala Ala Thr Met Ser Ser Arg Leu Ser His Lys Pro
865 870 875 880

Ser Asp Arg Pro Asn Gly Glu Ala Lys Thr Glu Leu Cys Glu Asn Val
885 890 895

Asp Pro Asn Ser Pro Ala Ala Lys Lys Lys Tyr Val Ser Tyr Asn Asn
900 905 910

Leu Val Ile
915

<210> 68
<211> 2748
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 68
atggtccagc tgaggaagct gctccgcgtc ctgactttga tgaagttccc ctgctgcgtg 60

ctggaggtgc tcctgtgcgc gctggcggcg gcggcgcgcg gccaggagat gtacgccccg 120

cactcaatcc ggatcgaggg ggacgtcacc ctcgggggggc tgttccccgt gcacgccaag 180

ggtcccagcg gagtgccctg cggcgacatc aagagggaaa acgggatcca caggctggaa 240

gcgatgctct acgccctgga ccagatcaac agtgatccca acctactgcc caacgtgacg 300

ctgggcgcgc ggatcctgga cacttgttcc agggacactt acgcgctcga acagtcgctt 360

actttcgtcc aggcgctcat ccagaaggac acctccgacg tgcgctgcac caacggcgaa 420

ccgccggttt tcgtcaagcc ggagaaagta gttggagtga ttggggcttc ggggagttcg 480

gtctccatca tggtagccaa catcctgagg ctcttccaga tccccccagat tagttatgca 540

tcaacggcac ccgagctaag tgatgaccgg cgctatgact tcttctctcg cgtggtgcca 600

cccgattcct tccaagccca ggccatggta gacattgtaa aggccctagg ctggaattat 660

gtgtctaccc tcgcatcgga aggaagttat ggagagaaag gtgtggagtc cttcacgcag 720

atttccaaag aggcaggtgg actctgcatt gcccagtccg tgagaatccc ccaggaacgc 780

aaagacagga ccattgactt tgatagaatt atcaaacagc tcctggacac ccccaactcc 840

agggccgtcg tgatttttgc caacgatgag gatataaagc agatccttgc agcagccaaa 900

agagctgacc aagttggcca ttttctttgg gtgggatcag acagctgggg atccaaaata 960

aacccactgc accagcatga agatatcgca gaaggggcca tcaccattca gcccaagcga 1020

gccacggtgg aagggtttga tgcctacttt acgtcccgta cacttgaaaa caacagaaga 1080

aatgtatggt ttgccgaata ctgggaggaa aacttcaact gcaagttgac gattagtggg 1140

tcaaaaaaag aagacacaga tcgcaaatgc acaggacagg agagaattgg aaaagattcc 1200

aactatgagc aggagggtaa agtccagttc gtgattgacg cagtctatgc tatggctcac 1260

gcccttcacc acatgaacaa ggatctctgt gctgactacc ggggtgtctg cccagagatg 1320

gagcaagctg gaggcaagaa gttgctgaag tatatacgca atgttaattt caatggtagt 1380

gctggcactc cagtgatgtt taacaagaac ggggatgcac ctgggcgtta tgacatcttt 1440

cagtaccaga ccacaaacac cagcaacccg ggttaccgtc tgatcgggca gtggacagac 1500

gaacttcagc tcaatataga agacatgcag tggggtaaag gagtccgaga gatacccgcc 1560

tcagtgtgca cactaccatg taagccagga cagagaaaga agacacagaa aggaactcct 1620

tgctgttgga cctgtgagcc ttgcgatggt taccagtacc agtttgatga gatgacatgc 1680

cagcattgcc cctatgacca gaggcccaat gaaaatcgaa ccggatgcca ggatattccc 1740

atcatcaaac tggagtggca ctccccctgg gctgtgattc ctgtcttcct ggcaatgttg 1800

gggatcattg ccaccatctt tgtcatggcc actttcatcc gctacaatga cacgcccatt 1860

gtccgggcat ctgggcggga actcagctat gttcttttga cgggcatctt tctttgctac 1920

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ttcttgggct tgggtatgtg catcagttat gcagccctct tgacgaaaac aaatcggatt 2040

tatcgcatat ttgagcaggg caagaaatca gtaacagctc ccagactcat aagcccaaca 2100

tcacaactgg caatcacttc cagtttaata tcagttcagc ttctaggggt gttcatttgg 2160

tttggtgttg atccacccaa catcatcata gactacgatg aacacaagac aatgaaccct 2220

gagcaagcca gaggggttct caagtgtgac attacagatc tccaaatcat ttgctccttg 2280

ggatatagca ttcttctcat ggtcacatgt actgtgtatg ccatcaagac tcggggtgta 2340

cccgagaatt ttaacgaagc caagcccatt ggattcacta tgtacacgac atgtatagta 2400

tggcttgcct tcattccaat ttttttggc accgctcaat cagcggaaaa gctctacata 2460

caaactacca cgcttacaat ctccatgaac ctaagtgcat cagtggcgct ggggatgcta 2520

tacatgccga aagtgtacat catcattttc caccctgaac tcaatgtcca gaaacggaag 2580

cgaagcttca aggcggtagt cacagcagcc accatgtcat cgaggctgtc acacaaaccc 2640

agtgacagac ccaacggtga ggcaaagacc gagctctgtg aaaacgtaga cccaaacagc 2700

cctgctgcaa aaaagaagta tgtcagttat aataacctgg ttatctaa 2748

<210> 69
<211> 915
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 69

Met Val Gln Leu Arg Lys Leu Leu Arg Val Leu Thr Leu Met Lys Phe
1 5 10 15

Pro Cys Cys Val Leu Glu Val Leu Leu Cys Ala Leu Ala Ala Ala Ala
20 25 30

Arg Gly Gln Glu Met Tyr Ala Pro His Ser Ile Arg Ile Glu Gly Asp
35 40 45

```
Val Thr Leu Gly Gly Leu Phe Pro Val His Ala Lys Gly Pro Ser Gly
    50                  55                  60

Val Pro Cys Gly Asp Ile Lys Arg Glu Asn Gly Ile His Arg Leu Glu
65                  70                  75                  80

Ala Met Leu Tyr Ala Leu Asp Gln Ile Asn Ser Asp Pro Asn Leu Leu
                85                  90                  95

Pro Asn Val Thr Leu Gly Ala Arg Ile Leu Asp Thr Cys Ser Arg Asp
            100                 105                 110

Thr Tyr Ala Leu Glu Gln Ser Leu Thr Phe Val Gln Ala Leu Ile Gln
        115                 120                 125

Lys Asp Thr Ser Asp Val Arg Cys Thr Asn Gly Glu Pro Pro Val Phe
    130                 135                 140

Val Lys Pro Glu Lys Val Val Gly Val Ile Gly Ala Ser Gly Ser Ser
145                 150                 155                 160

Val Ser Ile Met Val Ala Asn Ile Leu Arg Leu Phe Gln Ile Pro Gln
                165                 170                 175

Ile Ser Tyr Ala Ser Thr Ala Pro Glu Leu Ser Asp Asp Arg Arg Tyr
            180                 185                 190

Asp Phe Phe Ser Arg Val Val Pro Pro Asp Ser Phe Gln Ala Gln Ala
        195                 200                 205

Met Val Asp Ile Val Lys Ala Leu Gly Trp Asn Tyr Val Ser Thr Leu
    210                 215                 220

Ala Ser Glu Gly Ser Tyr Gly Glu Lys Gly Val Glu Ser Phe Thr Gln
225                 230                 235                 240

Ile Ser Lys Glu Ala Gly Gly Leu Cys Ile Ala Gln Ser Val Arg Ile
                245                 250                 255

Pro Gln Glu Arg Lys Asp Arg Thr Ile Asp Phe Asp Arg Ile Ile Lys
            260                 265                 270
```

```
Gln Leu Leu Asp Thr Pro Asn Ser Arg Ala Val Val Ile Phe Ala Asn
        275                 280                 285

Asp Glu Asp Ile Lys Gln Ile Leu Ala Ala Ala Lys Arg Ala Asp Gln
    290                 295                 300

Val Gly His Phe Leu Trp Val Gly Ser Asp Ser Trp Gly Ser Lys Ile
305                 310                 315                 320

Asn Pro Leu His Gln His Glu Asp Ile Ala Glu Gly Ala Ile Thr Ile
                325                 330                 335

Gln Pro Lys Arg Ala Thr Val Glu Gly Phe Asp Ala Tyr Phe Thr Ser
            340                 345                 350

Arg Thr Leu Glu Asn Asn Arg Arg Asn Val Trp Phe Ala Glu Tyr Trp
        355                 360                 365

Glu Glu Asn Phe Asn Cys Lys Leu Thr Ile Ser Gly Ser Lys Lys Glu
    370                 375                 380

Asp Thr Asp Arg Lys Cys Thr Gly Gln Glu Arg Ile Gly Lys Asp Ser
385                 390                 395                 400

Asn Tyr Glu Gln Glu Gly Lys Val Gln Phe Val Ile Asp Ala Val Tyr
                405                 410                 415

Ala Met Ala His Ala Leu His His Met Asn Lys Asp Leu Cys Ala Asp
            420                 425                 430

Tyr Arg Gly Val Cys Pro Glu Met Glu Gln Ala Gly Gly Lys Lys Leu
        435                 440                 445

Leu Lys Tyr Ile Arg Asn Val Asn Phe Asn Gly Ser Ala Gly Thr Pro
    450                 455                 460

Val Met Phe Asn Lys Asn Gly Asp Ala Pro Gly Arg Tyr Asp Ile Phe
465                 470                 475                 480

Gln Tyr Gln Thr Thr Asn Thr Ser Asn Pro Gly Tyr Arg Leu Ile Gly
                485                 490                 495
```

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Gln Trp Thr Asp Glu Leu Gln Leu Asn Ile Glu Asp Met Gln Trp Gly
            500                 505                 510

Lys Gly Val Arg Glu Ile Pro Ala Ser Val Cys Thr Leu Pro Cys Lys
        515                 520                 525

Pro Gly Gln Arg Lys Lys Thr Gln Lys Gly Thr Pro Cys Cys Trp Thr
    530                 535                 540

Cys Glu Pro Cys Asp Gly Tyr Gln Tyr Gln Phe Asp Glu Met Thr Cys
545                 550                 555                 560

Gln His Cys Pro Tyr Asp Gln Arg Pro Asn Glu Asn Arg Thr Gly Cys
                565                 570                 575

Gln Asp Ile Pro Ile Ile Lys Leu Glu Trp His Ser Pro Trp Ala Val
            580                 585                 590

Ile Pro Val Phe Leu Ala Met Leu Gly Ile Ile Ala Thr Ile Phe Val
        595                 600                 605

Met Ala Thr Phe Ile Arg Tyr Asn Asp Thr Pro Ile Val Arg Ala Ser
    610                 615                 620

Gly Arg Glu Leu Ser Tyr Val Leu Leu Thr Gly Ile Phe Leu Cys Tyr
625                 630                 635                 640

Ile Ile Thr Phe Leu Met Ile Ala Lys Pro Asp Val Ala Val Cys Ser
                645                 650                 655

Phe Arg His Val Phe Leu Gly Leu Gly Met Cys Ile Ser Tyr Ala Ala
            660                 665                 670

Leu Leu Thr Lys Thr Asn Arg Ile Tyr Arg Ile Phe Glu Gln Gly Lys
        675                 680                 685

Lys Ser Val Thr Ala Pro Arg Leu Ile Ser Pro Thr Ser Gln Leu Ala
    690                 695                 700

Ile Thr Ser Ser Leu Ile Ser Val Gln Leu Leu Gly Val Phe Ile Trp
705                 710                 715                 720

Phe Gly Val Asp Pro Pro Asn Ile Ile Ile Asp Tyr Asp Glu His Lys
```

725 730 735

Thr Met Asn Pro Glu Gln Ala Arg Gly Val Leu Lys Cys Asp Ile Thr
740 745 750

Asp Leu Gln Ile Ile Cys Ser Leu Gly Tyr Ser Ile Leu Leu Met Val
755 760 765

Thr Cys Thr Val Tyr Ala Ile Lys Thr Arg Gly Val Pro Glu Asn Phe
770 775 780

Asn Glu Ala Lys Pro Ile Gly Phe Thr Met Tyr Thr Thr Cys Ile Val
785 790 795 800

Trp Leu Ala Phe Ile Pro Ile Phe Phe Gly Thr Ala Gln Ser Ala Glu
805 810 815

Lys Leu Tyr Ile Gln Thr Thr Thr Leu Thr Ile Ser Met Asn Leu Ser
820 825 830

Ala Ser Val Ala Leu Gly Met Leu Tyr Met Pro Lys Val Tyr Ile Ile
835 840 845

Ile Phe His Pro Glu Leu Asn Val Gln Lys Arg Lys Arg Ser Phe Lys
850 855 860

Ala Val Val Thr Ala Ala Thr Met Ser Ser Arg Leu Ser His Lys Pro
865 870 875 880

Ser Asp Arg Pro Asn Gly Glu Ala Lys Thr Glu Leu Cys Glu Asn Val
885 890 895

Asp Pro Asn Ser Pro Ala Ala Lys Lys Lys Tyr Val Ser Tyr Asn Asn
900 905 910

Leu Val Ile
915

<210> 70
<211> 2748
<212> DNA
<213> Unknown

<220>

<223> Novel Sequence

<400> 70

atggtccagc tgaggaagct gctccgcgtc ctgactttga tgaagttccc ctgctgcgtg 60

ctggaggtgc tcctgtgcgc gctggcggcg gcggcgcgcg gccaggagat gtacgccccg 120

cactcaatcc ggatcgaggg ggacgtcacc ctcgggggggc tgttccccgt gcacgccaag 180

ggtcccagcg gagtgccctg cggcgacatc aagagggaaa acgggatcca caggctggaa 240

gcgatgctct acgccctgga ccagatcaac agtgatccca acctactgcc caacgtgacg 300

ctgggcgcgc ggatcctgga cacttgttcc agggacactt acgcgctcga acagtcgctt 360

actttcgtcc aggcgctcat ccagaaggac acctccgacg tgcgctgcac caacggcgaa 420

ccgccggttt tcgtcaagcc ggagaaagta gttggagtga ttggggcttc ggggagttcg 480

gtctccatca tggtagccaa catcctgagg ctcttccaga tcccccagat tagttatgca 540

tcaacggcac ccgagctaag tgatgaccgg cgctatgact tcttctctcg cgtggtgcca 600

cccgattcct tccaagccca ggccatggta gacattgtaa aggccctagg ctggaattat 660

gtgtctaccc tcgcatcgga aggaagttat ggagagaaag gtgtggagtc cttcacgcag 720

atttccaaag aggcaggtgg actctgcatt gcccagtccg tgagaatccc ccaggaacgc 780

aaagacagga ccattgactt tgatagaatt atcaaacagc tcctggacac ccccaactcc 840

agggccgtcg tgatttttgc caacgatgag gatataaagc agatccttgc agcagccaaa 900

agagctgacc aagttggcca ttttctttgg gtgggatcag acagctgggg atccaaaata 960

aacccactgc accagcatga agatatcgca gaaggggcca tcaccattca gcccaagcga 1020

gccacggtgg aagggtttga tgcctacttt acgtcccgta cacttgaaaa caacagaaga 1080

aatgtatggt ttgccgaata ctgggaggaa aacttcaact gcaagttgac gattagtggg 1140

tcaaaaaaag aagacacaga tcgcaaatgc acaggacagg agagaattgg aaaagattcc 1200

aactatgagc aggagggtaa agtccagttc gtgattgacg cagtctatgc tatggctcac 1260

gcccttcacc acatgaacaa ggatctctgt gctgactacc ggggtgtctg cccagagatg 1320

gagcaagctg gaggcaagaa gttgctgaag tatatacgca atgttaattt caatggtagt 1380

gctggcactc cagtgatgtt taacaagaac ggggatgcac ctgggcgtta tgacatcttt 1440

cagtaccaga ccacaaacac cagcaacccg ggttaccgtc tgatcgggca gtggacagac 1500

gaacttcagc tcaatataga agacatgcag tggggtaaag gagtccgaga gatacccgcc 1560

tcagtgtgca cactaccatg taagccagga cagagaaaga agacacagaa aggaactcct 1620

tgctgttgga cctgtgagcc ttgcgatggt taccagtacc agtttgatga gatgacatgc 1680

cagcattgcc cctatgacca gaggcccaat gaaaatcgaa ccggatgcca ggatattccc 1740

atcatcaaac tggagtggca ctccccctgg gctgtgattc ctgtcttcct ggcaatgttg 1800

gggatcattg ccaccatctt tgtcatggcc actttcatcc gctacaatga cacgcccatt 1860

gtccgggcat ctgggcggga actcagctat gttcttttga cgggcatctt tctttgctac 1920

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ttcttgggct tgggtatgtg catcagttat gcagccctct tgacgaaaac aaatcggatt 2040

tatcgcatat ttgagcaggg caagaaatca gtaacagctc ccagactcat aagcccaaca 2100

tcacaactgg caatcacttc cagtttaata tcagttcagc ttctaggggt gttcatttgg 2160

tttggtgttg atccacccaa catcatcata gactacgatg aacacaagac aatgaaccct 2220

gagcaagcca gaggggttct caagtgtgac attacagatc tccaaatcat ttgctccttg 2280

ggatatagca ttcttctcat ggtcacatgt tgtgtgtatg ccatcaagac tcggggtgta 2340

cccgagaatt ttaacgaagc caagcccatt ggattcacta tgtacacgac atgtatagta 2400

tggcttgcct tcattccaat ttttttggc accgctcaat cagcggaaaa gctctacata 2460

caaactacca cgcttacaat ctccatgaac ctaagtgcat cagtggcgct ggggatgcta 2520

tacatgccga aagtgtacat catcatttc caccctgaac tcaatgtcca gaaacggaag 2580

cgaagcttca aggcggtagt cacagcagcc accatgtcat cgaggctgtc acacaaaccc 2640

agtgacagac ccaacggtga ggcaaagacc gagctctgtg aaaacgtaga cccaaacagc 2700

cctgctgcaa aaaagaagta tgtcagttat aataacctgg ttatctaa 2748

<210> 71
<211> 915
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 71

Met Val Gln Leu Arg Lys Leu Leu Arg Val Leu Thr Leu Met Lys Phe
1 5 10 15

Pro Cys Cys Val Leu Glu Val Leu Leu Cys Ala Leu Ala Ala Ala Ala
20 25 30

```
Arg Gly Gln Glu Met Tyr Ala Pro His Ser Ile Arg Ile Glu Gly Asp
        35                  40                  45

Val Thr Leu Gly Gly Leu Phe Pro Val His Ala Lys Gly Pro Ser Gly
    50                  55                  60

Val Pro Cys Gly Asp Ile Lys Arg Glu Asn Gly Ile His Arg Leu Glu
65                  70                  75                  80

Ala Met Leu Tyr Ala Leu Asp Gln Ile Asn Ser Asp Pro Asn Leu Leu
                85                  90                  95

Pro Asn Val Thr Leu Gly Ala Arg Ile Leu Asp Thr Cys Ser Arg Asp
            100                 105                 110

Thr Tyr Ala Leu Glu Gln Ser Leu Thr Phe Val Gln Ala Leu Ile Gln
        115                 120                 125

Lys Asp Thr Ser Asp Val Arg Cys Thr Asn Gly Glu Pro Pro Val Phe
    130                 135                 140

Val Lys Pro Glu Lys Val Val Gly Val Ile Gly Ala Ser Gly Ser Ser
145                 150                 155                 160

Val Ser Ile Met Val Ala Asn Ile Leu Arg Leu Phe Gln Ile Pro Gln
                165                 170                 175

Ile Ser Tyr Ala Ser Thr Ala Pro Glu Leu Ser Asp Asp Arg Arg Tyr
            180                 185                 190

Asp Phe Phe Ser Arg Val Val Pro Pro Asp Ser Phe Gln Ala Gln Ala
        195                 200                 205

Met Val Asp Ile Val Lys Ala Leu Gly Trp Asn Tyr Val Ser Thr Leu
    210                 215                 220

Ala Ser Glu Gly Ser Tyr Gly Glu Lys Gly Val Glu Ser Phe Thr Gln
225                 230                 235                 240

Ile Ser Lys Glu Ala Gly Gly Leu Cys Ile Ala Gln Ser Val Arg Ile
                245                 250                 255

Pro Gln Glu Arg Lys Asp Arg Thr Ile Asp Phe Asp Arg Ile Ile Lys
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            260                 265                 270

Gln Leu Leu Asp Thr Pro Asn Ser Arg Ala Val Val Ile Phe Ala Asn
        275                 280                 285

Asp Glu Asp Ile Lys Gln Ile Leu Ala Ala Ala Lys Arg Ala Asp Gln
    290                 295                 300

Val Gly His Phe Leu Trp Val Gly Ser Asp Ser Trp Gly Ser Lys Ile
305                 310                 315                 320

Asn Pro Leu His Gln His Glu Asp Ile Ala Glu Gly Ala Ile Thr Ile
                325                 330                 335

Gln Pro Lys Arg Ala Thr Val Glu Gly Phe Asp Ala Tyr Phe Thr Ser
            340                 345                 350

Arg Thr Leu Glu Asn Asn Arg Arg Asn Val Trp Phe Ala Glu Tyr Trp
        355                 360                 365

Glu Glu Asn Phe Asn Cys Lys Leu Thr Ile Ser Gly Ser Lys Lys Glu
    370                 375                 380

Asp Thr Asp Arg Lys Cys Thr Gly Gln Glu Arg Ile Gly Lys Asp Ser
385                 390                 395                 400

Asn Tyr Glu Gln Glu Gly Lys Val Gln Phe Val Ile Asp Ala Val Tyr
                405                 410                 415

Ala Met Ala His Ala Leu His His Met Asn Lys Asp Leu Cys Ala Asp
            420                 425                 430

Tyr Arg Gly Val Cys Pro Glu Met Glu Gln Ala Gly Gly Lys Lys Leu
        435                 440                 445

Leu Lys Tyr Ile Arg Asn Val Asn Phe Asn Gly Ser Ala Gly Thr Pro
    450                 455                 460

Val Met Phe Asn Lys Asn Gly Asp Ala Pro Gly Arg Tyr Asp Ile Phe
465                 470                 475                 480

Gln Tyr Gln Thr Thr Asn Thr Ser Asn Pro Gly Tyr Arg Leu Ile Gly
                485                 490                 495
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Gln Trp Thr Asp Glu Leu Gln Leu Asn Ile Glu Asp Met Gln Trp Gly
            500                 505                 510

Lys Gly Val Arg Glu Ile Pro Ala Ser Val Cys Thr Leu Pro Cys Lys
        515                 520                 525

Pro Gly Gln Arg Lys Lys Thr Gln Lys Gly Thr Pro Cys Cys Trp Thr
    530                 535                 540

Cys Glu Pro Cys Asp Gly Tyr Gln Tyr Gln Phe Asp Glu Met Thr Cys
545                 550                 555                 560

Gln His Cys Pro Tyr Asp Gln Arg Pro Asn Glu Asn Arg Thr Gly Cys
                565                 570                 575

Gln Asp Ile Pro Ile Ile Lys Leu Glu Trp His Ser Pro Trp Ala Val
            580                 585                 590

Ile Pro Val Phe Leu Ala Met Leu Gly Ile Ile Ala Thr Ile Phe Val
        595                 600                 605

Met Ala Thr Phe Ile Arg Tyr Asn Asp Thr Pro Ile Val Arg Ala Ser
    610                 615                 620

Gly Arg Glu Leu Ser Tyr Val Leu Leu Thr Gly Ile Phe Leu Cys Tyr
625                 630                 635                 640

Ile Ile Thr Phe Leu Met Ile Ala Lys Pro Asp Val Ala Val Cys Ser
                645                 650                 655

Phe Arg Arg Val Phe Leu Gly Leu Gly Met Cys Ile Ser Tyr Ala Ala
            660                 665                 670

Leu Leu Thr Lys Thr Asn Arg Ile Tyr Arg Ile Phe Glu Gln Gly Lys
        675                 680                 685

Lys Ser Val Thr Ala Pro Arg Leu Ile Ser Pro Thr Ser Gln Leu Ala
    690                 695                 700

Ile Thr Ser Ser Leu Ile Ser Val Gln Leu Leu Gly Val Phe Ile Trp
705                 710                 715                 720
```

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Phe Gly Val Asp Pro Pro Asn Ile Ile Ile Asp Tyr Asp Glu His Lys
                725                 730                 735

Thr Met Asn Pro Glu Gln Ala Arg Gly Val Leu Lys Cys Asp Ile Thr
            740                 745                 750

Asp Leu Gln Ile Ile Cys Ser Leu Gly Tyr Ser Ile Leu Leu Met Val
        755                 760                 765

Thr Cys Cys Val Tyr Ala Ile Lys Thr Arg Gly Val Pro Glu Asn Phe
    770                 775                 780

Asn Glu Ala Lys Pro Ile Gly Phe Thr Met Tyr Thr Thr Cys Ile Val
785                 790                 795                 800

Trp Leu Ala Phe Ile Pro Ile Phe Phe Gly Thr Ala Gln Ser Ala Glu
                805                 810                 815

Lys Leu Tyr Ile Gln Thr Thr Thr Leu Thr Ile Ser Met Asn Leu Ser
            820                 825                 830

Ala Ser Val Ala Leu Gly Met Leu Tyr Met Pro Lys Val Tyr Ile Ile
        835                 840                 845

Ile Phe His Pro Glu Leu Asn Val Gln Lys Arg Lys Arg Ser Phe Lys
    850                 855                 860

Ala Val Val Thr Ala Ala Thr Met Ser Ser Arg Leu Ser His Lys Pro
865                 870                 875                 880

Ser Asp Arg Pro Asn Gly Glu Ala Lys Thr Glu Leu Cys Glu Asn Val
                885                 890                 895

Asp Pro Asn Ser Pro Ala Ala Lys Lys Lys Tyr Val Ser Tyr Asn Asn
            900                 905                 910

Leu Val Ile
        915
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<210> 72
<211> 2748
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 72
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cactcaatcc ggatcgaggg ggacgtcacc ctcgggggggc tgttccccgt gcacgccaag 180

ggtcccagcg gagtgccctg cggcgacatc aagagggaaa acgggatcca caggctggaa 240

gcgatgctct acgccctgga ccagatcaac agtgatccca acctactgcc caacgtgacg 300

ctgggcgcgc ggatcctgga cacttgttcc agggacactt acgcgctcga acagtcgctt 360

actttcgtcc aggcgctcat ccagaaggac acctccgacg tgcgctgcac caacggcgaa 420

ccgccggttt tcgtcaagcc ggagaaagta gttggagtga ttggggcttc ggggagttcg 480

gtctccatca tggtagccaa catcctgagg ctcttccaga tcccccagat tagttatgca 540

tcaacggcac ccgagctaag tgatgaccgg cgctatgact tcttctctcg cgtggtgcca 600

cccgattcct tccaagccca ggccatggta gacattgtaa aggccctagg ctggaattat 660

gtgtctaccc tcgcatcgga aggaagttat ggagagaaag gtgtggagtc cttcacgcag 720

atttccaaag aggcaggtgg actctgcatt gcccagtccg tgagaatccc ccaggaacgc 780

aaagacagga ccattgactt tgatagaatt atcaaacagc tcctggacac ccccaactcc 840

agggccgtcg tgatttttgc caacgatgag gatataaagc agatccttgc agcagccaaa 900

agagctgacc aagttggcca ttttctttgg gtgggatcag acagctgggg atccaaaata 960

aacccactgc accagcatga agatatcgca gaaggggcca tcaccattca gcccaagcga 1020

gccacggtgg aagggtttga tgcctacttt acgtcccgta cacttgaaaa caacagaaga 1080

aatgtatggt ttgccgaata ctgggaggaa aacttcaact gcaagttgac gattagtggg 1140

tcaaaaaaag aagacacaga tcgcaaatgc acaggacagg agagaattgg aaaagattcc 1200

aactatgagc aggagggtaa agtccagttc gtgattgacg cagtctatgc tatggctcac 1260

gcccttcacc acatgaacaa ggatctctgt gctgactacc ggggtgtctg cccagagatg 1320

gagcaagctg gaggcaagaa gttgctgaag tatatacgca atgttaattt caatggtagt 1380

gctggcactc cagtgatgtt taacaagaac ggggatgcac ctgggcgtta tgacatcttt 1440

cagtaccaga ccacaaacac cagcaacccg ggttaccgtc tgatcgggca gtggacagac 1500

gaacttcagc tcaatataga agacatgcag tggggtaaag gagtccgaga gatacccgcc 1560

tcagtgtgca cactaccatg taagccagga cagagaaaga agacacagaa aggaactcct 1620

tgctgttgga cctgtgagcc ttgcgatggt taccagtacc agtttgatga gatgacatgc 1680

cagcattgcc cctatgacca gaggcccaat gaaaatcgaa ccggatgcca ggatattccc 1740

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gggatcattg ccaccatctt tgtcatggcc actttcatcc gctacaatga cacgcccatt 1860

gtccgggcat ctgggcggga actcagctat gttcttttga cgggcatctt tctttgctac 1920

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ttcttgggct tgggtatgtg catcagttat gcagccctct tgacgaaaac aaatcggatt 2040

tatcgcatat ttgagcaggg caagaaatca gtaacagctc ccagactcat aagcccaaca 2100

tcacaactgg caatcacttc cagtttaata tcagttcagc ttctaggggt gttcatttgg 2160

tttggtgttg atccacccaa catcatcata gactacgatg aacacaagac aatgaaccct 2220

gagcaagcca gaggggttct caagtgtgac attacagatc tccaaatcat ttgctccttg 2280

ggatatagca ttcttctcat ggtcacatgt actgtgtatg ccatcaagac tcggggtgta 2340

cccgagaatt ttaacgaagc caagcccaag ggattcacta tgtacacgac atgtatagta 2400

tggcttgcct tcattccaat tttttttggc accgctcaat cagcggaaaa gctctacata 2460

caaactacca cgcttacaat ctccatgaac ctaagtgcat cagtggcgct ggggatgcta 2520

tacatgccga aagtgtacat catcattttc caccctgaac tcaatgtcca gaaacggaag 2580

cgaagcttca aggcggtagt cacagcagcc accatgtcat cgaggctgtc acacaaaccc 2640

agtgacagac ccaacggtga ggcaaagacc gagctctgtg aaaacgtaga cccaaacagc 2700

cctgctgcaa aaaagaagta tgtcagttat aataacctgg ttatctaa 2748

<210> 73
<211> 915
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 73

Met Val Gln Leu Arg Lys Leu Leu Arg Val Leu Thr Leu Met Lys Phe
1 5 10 15

Pro Cys Cys Val Leu Glu Val Leu Leu Cys Ala Leu Ala Ala Ala Ala
20 25 30

```
Arg Gly Gln Glu Met Tyr Ala Pro His Ser Ile Arg Ile Glu Gly Asp
        35                  40                  45

Val Thr Leu Gly Gly Leu Phe Pro Val His Ala Lys Gly Pro Ser Gly
    50                  55                  60

Val Pro Cys Gly Asp Ile Lys Arg Glu Asn Gly Ile His Arg Leu Glu
65                  70                  75                  80

Ala Met Leu Tyr Ala Leu Asp Gln Ile Asn Ser Asp Pro Asn Leu Leu
                85                  90                  95

Pro Asn Val Thr Leu Gly Ala Arg Ile Leu Asp Thr Cys Ser Arg Asp
            100                 105                 110

Thr Tyr Ala Leu Glu Gln Ser Leu Thr Phe Val Gln Ala Leu Ile Gln
        115                 120                 125

Lys Asp Thr Ser Asp Val Arg Cys Thr Asn Gly Glu Pro Pro Val Phe
    130                 135                 140

Val Lys Pro Glu Lys Val Val Gly Val Ile Gly Ala Ser Gly Ser Ser
145                 150                 155                 160

Val Ser Ile Met Val Ala Asn Ile Leu Arg Leu Phe Gln Ile Pro Gln
                165                 170                 175

Ile Ser Tyr Ala Ser Thr Ala Pro Glu Leu Ser Asp Asp Arg Arg Tyr
            180                 185                 190

Asp Phe Phe Ser Arg Val Val Pro Pro Asp Ser Phe Gln Ala Gln Ala
        195                 200                 205

Met Val Asp Ile Val Lys Ala Leu Gly Trp Asn Tyr Val Ser Thr Leu
    210                 215                 220

Ala Ser Glu Gly Ser Tyr Gly Glu Lys Gly Val Glu Ser Phe Thr Gln
225                 230                 235                 240

Ile Ser Lys Glu Ala Gly Gly Leu Cys Ile Ala Gln Ser Val Arg Ile
                245                 250                 255
```

```
Pro Gln Glu Arg Lys Asp Arg Thr Ile Asp Phe Asp Arg Ile Ile Lys
            260                 265                 270

Gln Leu Leu Asp Thr Pro Asn Ser Arg Ala Val Val Ile Phe Ala Asn
        275                 280                 285

Asp Glu Asp Ile Lys Gln Ile Leu Ala Ala Ala Lys Arg Ala Asp Gln
    290                 295                 300

Val Gly His Phe Leu Trp Val Gly Ser Asp Ser Trp Gly Ser Lys Ile
305                 310                 315                 320

Asn Pro Leu His Gln His Glu Asp Ile Ala Glu Gly Ala Ile Thr Ile
                325                 330                 335

Gln Pro Lys Arg Ala Thr Val Glu Gly Phe Asp Ala Tyr Phe Thr Ser
            340                 345                 350

Arg Thr Leu Glu Asn Asn Arg Arg Asn Val Trp Phe Ala Glu Tyr Trp
        355                 360                 365

Glu Glu Asn Phe Asn Cys Lys Leu Thr Ile Ser Gly Ser Lys Lys Glu
    370                 375                 380

Asp Thr Asp Arg Lys Cys Thr Gly Gln Glu Arg Ile Gly Lys Asp Ser
385                 390                 395                 400

Asn Tyr Glu Gln Glu Gly Lys Val Gln Phe Val Ile Asp Ala Val Tyr
                405                 410                 415

Ala Met Ala His Ala Leu His His Met Asn Lys Asp Leu Cys Ala Asp
            420                 425                 430

Tyr Arg Gly Val Cys Pro Glu Met Glu Gln Ala Gly Gly Lys Lys Leu
        435                 440                 445

Leu Lys Tyr Ile Arg Asn Val Asn Phe Asn Gly Ser Ala Gly Thr Pro
    450                 455                 460

Val Met Phe Asn Lys Asn Gly Asp Ala Pro Gly Arg Tyr Asp Ile Phe
465                 470                 475                 480
```

```
Gln Tyr Gln Thr Thr Asn Thr Ser Asn Pro Gly Tyr Arg Leu Ile Gly
                485                 490                 495

Gln Trp Thr Asp Glu Leu Gln Leu Asn Ile Glu Asp Met Gln Trp Gly
            500                 505                 510

Lys Gly Val Arg Glu Ile Pro Ala Ser Val Cys Thr Leu Pro Cys Lys
        515                 520                 525

Pro Gly Gln Arg Lys Lys Thr Gln Lys Gly Thr Pro Cys Cys Trp Thr
    530                 535                 540

Cys Glu Pro Cys Asp Gly Tyr Gln Tyr Gln Phe Asp Glu Met Thr Cys
545                 550                 555                 560

Gln His Cys Pro Tyr Asp Gln Arg Pro Asn Glu Asn Arg Thr Gly Cys
                565                 570                 575

Gln Asp Ile Pro Ile Ile Lys Leu Glu Trp His Ser Pro Trp Ala Val
            580                 585                 590

Ile Pro Val Phe Leu Ala Met Leu Gly Ile Ile Ala Thr Ile Phe Val
        595                 600                 605

Met Ala Thr Phe Ile Arg Tyr Asn Asp Thr Pro Ile Val Arg Ala Ser
    610                 615                 620

Gly Arg Glu Leu Ser Tyr Val Leu Leu Thr Gly Ile Phe Leu Cys Tyr
625                 630                 635                 640

Ile Ile Thr Phe Leu Met Ile Ala Lys Pro Asp Val Ala Val Cys Ser
                645                 650                 655

Phe Arg Arg Val Phe Leu Gly Leu Gly Met Cys Ile Ser Tyr Ala Ala
            660                 665                 670

Leu Leu Thr Lys Thr Asn Arg Ile Tyr Arg Ile Phe Glu Gln Gly Lys
        675                 680                 685

Lys Ser Val Thr Ala Pro Arg Leu Ile Ser Pro Thr Ser Gln Leu Ala
    690                 695                 700

Ile Thr Ser Ser Leu Ile Ser Val Gln Leu Leu Gly Val Phe Ile Trp
```

705 710 715 720

Phe Gly Val Asp Pro Pro Asn Ile Ile Ile Asp Tyr Asp Glu His Lys
725 730 735

Thr Met Asn Pro Glu Gln Ala Arg Gly Val Leu Lys Cys Asp Ile Thr
740 745 750

Asp Leu Gln Ile Ile Cys Ser Leu Gly Tyr Ser Ile Leu Leu Met Val
755 760 765

Thr Cys Thr Val Tyr Ala Ile Lys Thr Arg Gly Val Pro Glu Asn Phe
770 775 780

Asn Glu Ala Lys Pro Lys Gly Phe Thr Met Tyr Thr Thr Cys Ile Val
785 790 795 800

Trp Leu Ala Phe Ile Pro Ile Phe Phe Gly Thr Ala Gln Ser Ala Glu
805 810 815

Lys Leu Tyr Ile Gln Thr Thr Thr Leu Thr Ile Ser Met Asn Leu Ser
820 825 830

Ala Ser Val Ala Leu Gly Met Leu Tyr Met Pro Lys Val Tyr Ile Ile
835 840 845

Ile Phe His Pro Glu Leu Asn Val Gln Lys Arg Lys Arg Ser Phe Lys
850 855 860

Ala Val Val Thr Ala Ala Thr Met Ser Ser Arg Leu Ser His Lys Pro
865 870 875 880

Ser Asp Arg Pro Asn Gly Glu Ala Lys Thr Glu Leu Cys Glu Asn Val
885 890 895

Asp Pro Asn Ser Pro Ala Ala Lys Lys Lys Tyr Val Ser Tyr Asn Asn
900 905 910

Leu Val Ile
915

<210> 74
<211> 1842

<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 74
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ggggagagct gtgcacctac agtgatccag cgccgcggca gggacgcctg gggaccggga 180

aattctgcaa gagacgttct gcgagcccga gcacccaggg aggagcaggg ggcagcgttt 240

cttgcgggac cctcctggga cctgccggcg gccccgggcc gtgacccggc tgcaggcaga 300

ggggcggagg cgtcggcagc cggacccccg ggacctccaa ccaggccacc tggcccctgg 360

aggtggaaag gtgctcgggg tcaggagcct tctgaaactt tggggagagg gaaccccacg 420

gccctccagc tcttccttca gatctcagag gaggaagaga agggtcccag aggcgctggc 480

atttccgggc gtagccagga gcagagtgtg aagacagtcc ccggagccag cgatcttttt 540

tactggccaa ggagagccgg gaaactccag ggttcccacc acaagcccct gtccaagacg 600

gccaatggac tggcggggca cgaagggtgg acaattgcac tcccgggccg ggcgctggcc 660

cagaatggat ccttgggtga aggaatccat gagcctgggg gtccccgccg gggaaacagc 720

acgaaccggc gtgtgagact gaagaacccc ttctacccgc tgacccagga gtcctatgga 780

gcctacgcgg tcatgtgtct gtccgtggtg atcttcggga ccggcatcat tggcaacctg 840

gcggtgatgt gcatcgtgtg ccacaactac tacatgcgga gcatctccaa ctcccttctg 900

gccaacctgg ccttctggga ctttctcatc atcttcttct gccttccgct ggtcatcttc 960

cacgagctga ccaagaagtg gctgctggag gacttctcct gcaagatcgt gccctatata 1020

gaggtcgctt ctctgggagt caccaccttc acccgatgtg ctctgtgcat agaccgcttc 1080

cgtgctgcca ccaacgtaca gatgtactac gaaatgatcg aaaactgttc ctcaacaact 1140

gccaaacttg ctgttatatg ggtgggagct ctattgttag cacttccaga agttgttctc 1200

cgccagctga gcaaggagga tttggggttt agtggccgag ctccggcaga aaggtgcatt 1260

attaagatct ctcctgattt accagacacc atctatgttc tagccctcac ctacgacagt 1320

gcgagactgt ggtggtattt tggctgttac ttttgtttgc ccacgctttt caccatcacc 1380

tgctctctag tgactgcgag gaaaatccgc aaagcagaga aagcctgtac ccgagggaat 1440

aaacggcaga ttcaactaga gagtcagatg aactgtacag tagtggcact gaccatttta 1500

tatggatttt gcattattcc tgaaaatatc tgcaacattg ttactgccta catggctaca 1560

ggggtttcac agcagacaat ggacctcctt aatatcatca gccagttcct tttgttcttt 1620

aagtcctgtg tcaccccagt cctccttttc tgtctctgca aacccttcag tcgggccttc 1680

atggagtgct gctgctgttg ctgtgaggaa tgcattcaga agtcttcaac ggtgaccagt 1740

gatgacaatg acaacgagta caccacggaa ctcgaactct cgcctttcag taccatacgc 1800

cgtgaaatgt ccacttttgc ttctgtcgga actcattgct ga 1842

<210> 75
<211> 613
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 75

Met Arg Ala Pro Gly Ala Leu Leu Ala Arg Met Ser Arg Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Lys Val Ser Ala Ser Ser Ala Leu Gly Val Ala Pro
20 25 30

Ala Ser Arg Asn Glu Thr Cys Leu Gly Glu Ser Cys Ala Pro Thr Val
35 40 45

Ile Gln Arg Arg Gly Arg Asp Ala Trp Gly Pro Gly Asn Ser Ala Arg
50 55 60

Asp Val Leu Arg Ala Arg Ala Pro Arg Glu Glu Gln Gly Ala Ala Phe
65 70 75 80

Leu Ala Gly Pro Ser Trp Asp Leu Pro Ala Ala Pro Gly Arg Asp Pro
85 90 95

Ala Ala Gly Arg Gly Ala Glu Ala Ser Ala Ala Gly Pro Pro Gly Pro
100 105 110

Pro Thr Arg Pro Pro Gly Pro Trp Arg Trp Lys Gly Ala Arg Gly Gln
115 120 125

Glu Pro Ser Glu Thr Leu Gly Arg Gly Asn Pro Thr Ala Leu Gln Leu
130 135 140

```
Phe Leu Gln Ile Ser Glu Glu Glu Glu Lys Gly Pro Arg Gly Ala Gly
145                 150                 155                 160

Ile Ser Gly Arg Ser Gln Glu Gln Ser Val Lys Thr Val Pro Gly Ala
                165                 170                 175

Ser Asp Leu Phe Tyr Trp Pro Arg Arg Ala Gly Lys Leu Gln Gly Ser
            180                 185                 190

His His Lys Pro Leu Ser Lys Thr Ala Asn Gly Leu Ala Gly His Glu
        195                 200                 205

Gly Trp Thr Ile Ala Leu Pro Gly Arg Ala Leu Ala Gln Asn Gly Ser
    210                 215                 220

Leu Gly Glu Gly Ile His Glu Pro Gly Gly Pro Arg Arg Gly Asn Ser
225                 230                 235                 240

Thr Asn Arg Arg Val Arg Leu Lys Asn Pro Phe Tyr Pro Leu Thr Gln
                245                 250                 255

Glu Ser Tyr Gly Ala Tyr Ala Val Met Cys Leu Ser Val Val Ile Phe
            260                 265                 270

Gly Thr Gly Ile Ile Gly Asn Leu Ala Val Met Cys Ile Val Cys His
        275                 280                 285

Asn Tyr Tyr Met Arg Ser Ile Ser Asn Ser Leu Leu Ala Asn Leu Ala
    290                 295                 300

Phe Trp Asp Phe Leu Ile Ile Phe Phe Cys Leu Pro Leu Val Ile Phe
305                 310                 315                 320

His Glu Leu Thr Lys Lys Trp Leu Leu Glu Asp Phe Ser Cys Lys Ile
                325                 330                 335

Val Pro Tyr Ile Glu Val Ala Ser Leu Gly Val Thr Thr Phe Thr Arg
            340                 345                 350

Cys Ala Leu Cys Ile Asp Arg Phe Arg Ala Ala Thr Asn Val Gln Met
        355                 360                 365
```

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Tyr Tyr Glu Met Ile Glu Asn Cys Ser Ser Thr Thr Ala Lys Leu Ala
    370                 375                 380

Val Ile Trp Val Gly Ala Leu Leu Leu Ala Leu Pro Glu Val Val Leu
385                 390                 395                 400

Arg Gln Leu Ser Lys Glu Asp Leu Gly Phe Ser Gly Arg Ala Pro Ala
                405                 410                 415

Glu Arg Cys Ile Ile Lys Ile Ser Pro Asp Leu Pro Asp Thr Ile Tyr
            420                 425                 430

Val Leu Ala Leu Thr Tyr Asp Ser Ala Arg Leu Trp Trp Tyr Phe Gly
        435                 440                 445

Cys Tyr Phe Cys Leu Pro Thr Leu Phe Thr Ile Thr Cys Ser Leu Val
    450                 455                 460

Thr Ala Arg Lys Ile Arg Lys Ala Glu Lys Ala Cys Thr Arg Gly Asn
465                 470                 475                 480

Lys Arg Gln Ile Gln Leu Glu Ser Gln Met Asn Cys Thr Val Val Ala
                485                 490                 495

Leu Thr Ile Leu Tyr Gly Phe Cys Ile Ile Pro Glu Asn Ile Cys Asn
            500                 505                 510

Ile Val Thr Ala Tyr Met Ala Thr Gly Val Ser Gln Gln Thr Met Asp
        515                 520                 525

Leu Leu Asn Ile Ile Ser Gln Phe Leu Leu Phe Phe Lys Ser Cys Val
    530                 535                 540

Thr Pro Val Leu Leu Phe Cys Leu Cys Lys Pro Phe Ser Arg Ala Phe
545                 550                 555                 560

Met Glu Cys Cys Cys Cys Cys Cys Glu Glu Cys Ile Gln Lys Ser Ser
                565                 570                 575

Thr Val Thr Ser Asp Asp Asn Asp Asn Glu Tyr Thr Thr Glu Leu Glu
            580                 585                 590
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Leu Ser Pro Phe Ser Thr Ile Arg Arg Glu Met Ser Thr Phe Ala Ser
595 600 605

Val Gly Thr His Cys
610

<210> 76
<211> 1842
<212> DNA
<213> Homo sapiens

<400> 76
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aaggtgtctg cctcttctgc cctcggggtc gcccctgcgt ccagaaacga aacttgtctg 120

ggggagagct gtgcacctac agtgatccag cgccgcggca gggacgcctg gggaccggga 180

aattctgcaa gagacgttct gcgagcccga gcacccaggg aggagcaggg ggcagcgttt 240

cttgcgggac cctcctggga cctgccggcg gccccgggcc gtgacccggc tgcaggcaga 300

ggggcggagg cgtcggcagc cggacccccg ggacctccaa ccaggccacc tggcccctgg 360

aggtggaaag gtgctcgggg tcaggagcct tctgaaactt tggggagagg gaaccccacg 420

gccctccagc tcttccttca gatctcagag gaggaagaga agggtcccag aggcgctggc 480

atttccgggc gtagccagga gcagagtgtg aagacagtcc ccggagccag cgatcttttt 540

tactggccaa ggagagccgg gaaactccag ggttcccacc acaagcccct gtccaagacg 600

gccaatggac tggcggggca cgaagggtgg acaattgcac tcccgggccg ggcgctggcc 660

cagaatggat ccttgggtga aggaatccat gagcctgggg gtccccgccg gggaaacagc 720

acgaaccggc gtgtgagact gaagaacccc ttctacccgc tgacccagga gtcctatgga 780

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cacgagctga ccaagaagtg gctgctggag gacttctcct gcaagatcgt gccctatata 1020

gaggtcgctt ctctgggagt caccaccttc accttatgtg ctctgtgcat agaccgcttc 1080

cgtgctgcca ccaacgtaca gatgtactac gaaatgatcg aaaactgttc ctcaacaact 1140

gccaaacttg ctgttatatg ggtgggagct ctattgttag cacttccaga agttgttctc 1200

cgccagctga gcaaggagga tttggggttt agtggccgag ctccggcaga aaggtgcatt 1260

attaagatct ctcctgattt accagacacc atctatgttc tagccctcac ctacgacagt 1320

gcgagactgt ggtggtattt tggctgttac ttttgtttgc ccacgctttt caccatcacc 1380

tgctctctag tgactgcgag gaaaatccgc aaagcagaga aagcctgtac ccgagggaat 1440

aaacggcaga ttcaactaga gagtcagatg aactgtacag tagtggcact gaccatttta 1500

tatggatttt gcattattcc tgaaaatatc tgcaacattg ttactgccta catggctaca 1560

ggggtttcac agcagacaat ggacctcctt aatatcatca gccagttcct tttgttcttt 1620

aagtcctatg tcaccccagt cctccttttc tgtctctgca aacccttcag tcgggccttc 1680

atggagtgct gctgctgttg ctgtgaggaa tgcattcaga agtcttcaac ggtgaccagt 1740

gatgacaatg acaacgagta caccacggaa ctcgaactct cgcctttcag taccatacgc 1800

cgtgaaatgt ccacttttgc ttctgtcgga actcattgct ga 1842

<210> 77
<211> 613
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 77

Met Arg Ala Pro Gly Ala Leu Leu Ala Arg Met Ser Arg Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Lys Val Ser Ala Ser Ser Ala Leu Gly Val Ala Pro
20 25 30

Ala Ser Arg Asn Glu Thr Cys Leu Gly Glu Ser Cys Ala Pro Thr Val
35 40 45

Ile Gln Arg Arg Gly Arg Asp Ala Trp Gly Pro Gly Asn Ser Ala Arg
50 55 60

Asp Val Leu Arg Ala Arg Ala Pro Arg Glu Glu Gln Gly Ala Ala Phe
65 70 75 80

Leu Ala Gly Pro Ser Trp Asp Leu Pro Ala Ala Pro Gly Arg Asp Pro
85 90 95

Ala Ala Gly Arg Gly Ala Glu Ala Ser Ala Ala Gly Pro Pro Gly Pro
100 105 110

```
Pro Thr Arg Pro Pro Gly Pro Trp Arg Trp Lys Gly Ala Arg Gly Gln
        115                 120                 125

Glu Pro Ser Glu Thr Leu Gly Arg Gly Asn Pro Thr Ala Leu Gln Leu
    130                 135                 140

Phe Leu Gln Ile Ser Glu Glu Glu Glu Lys Gly Pro Arg Gly Ala Gly
145                 150                 155                 160

Ile Ser Gly Arg Ser Gln Glu Gln Ser Val Lys Thr Val Pro Gly Ala
                165                 170                 175

Ser Asp Leu Phe Tyr Trp Pro Arg Arg Ala Gly Lys Leu Gln Gly Ser
            180                 185                 190

His His Lys Pro Leu Ser Lys Thr Ala Asn Gly Leu Ala Gly His Glu
        195                 200                 205

Gly Trp Thr Ile Ala Leu Pro Gly Arg Ala Leu Ala Gln Asn Gly Ser
    210                 215                 220

Leu Gly Glu Gly Ile His Glu Pro Gly Gly Pro Arg Arg Gly Asn Ser
225                 230                 235                 240

Thr Asn Arg Arg Val Arg Leu Lys Asn Pro Phe Tyr Pro Leu Thr Gln
                245                 250                 255

Glu Ser Tyr Gly Ala Tyr Ala Val Met Cys Leu Ser Val Val Ile Phe
            260                 265                 270

Gly Thr Gly Ile Ile Gly Asn Leu Ala Val Met Cys Ile Val Cys His
        275                 280                 285

Asn Tyr Tyr Met Arg Ser Ile Ser Asn Ser Leu Leu Ala Asn Leu Ala
    290                 295                 300

Phe Trp Asp Phe Leu Ile Ile Phe Phe Cys Leu Pro Leu Val Ile Phe
305                 310                 315                 320

His Glu Leu Thr Lys Lys Trp Leu Leu Glu Asp Phe Ser Cys Lys Ile
                325                 330                 335
```

Val Pro Tyr Ile Glu Val Ala Ser Leu Gly Val Thr Thr Phe Thr Leu
340 345 350

Cys Ala Leu Cys Ile Asp Arg Phe Arg Ala Ala Thr Asn Val Gln Met
355 360 365

Tyr Tyr Glu Met Ile Glu Asn Cys Ser Ser Thr Thr Ala Lys Leu Ala
370 375 380

Val Ile Trp Val Gly Ala Leu Leu Leu Ala Leu Pro Glu Val Val Leu
385 390 395 400

Arg Gln Leu Ser Lys Glu Asp Leu Gly Phe Ser Gly Arg Ala Pro Ala
405 410 415

Glu Arg Cys Ile Ile Lys Ile Ser Pro Asp Leu Pro Asp Thr Ile Tyr
420 425 430

Val Leu Ala Leu Thr Tyr Asp Ser Ala Arg Leu Trp Trp Tyr Phe Gly
435 440 445

Cys Tyr Phe Cys Leu Pro Thr Leu Phe Thr Ile Thr Cys Ser Leu Val
450 455 460

Thr Ala Arg Lys Ile Arg Lys Ala Glu Lys Ala Cys Thr Arg Gly Asn
465 470 475 480

Lys Arg Gln Ile Gln Leu Glu Ser Gln Met Asn Cys Thr Val Val Ala
485 490 495

Leu Thr Ile Leu Tyr Gly Phe Cys Ile Ile Pro Glu Asn Ile Cys Asn
500 505 510

Ile Val Thr Ala Tyr Met Ala Thr Gly Val Ser Gln Gln Thr Met Asp
515 520 525

Leu Leu Asn Ile Ile Ser Gln Phe Leu Leu Phe Phe Lys Ser Tyr Val
530 535 540

Thr Pro Val Leu Leu Phe Cys Leu Cys Lys Pro Phe Ser Arg Ala Phe
545 550 555 560

Met Glu Cys Cys Cys Cys Cys Cys Glu Glu Cys Ile Gln Lys Ser Ser

565 570 575

Thr Val Thr Ser Asp Asp Asn Asp Asn Glu Tyr Thr Thr Glu Leu Glu
580 585 590

Leu Ser Pro Phe Ser Thr Ile Arg Arg Glu Met Ser Thr Phe Ala Ser
595 600 605

Val Gly Thr His Cys
610

<210> 78
<211> 1086
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 78
atgtcccctg aatgcgcgcg ggcagcgggc gacgcgccct tgcgcagcct ggagcaagcc 60

aaccgcaccc gctttccctt cttctccgac gtcaagggcg accaccggct ggtgctggcc 120

gcggtggaga caaccgtgct ggtgctcatc tttgcagtgt cgctgctggg caacgtgtgc 180

gccctggtgc tggtggcgcg ccgacgacgc cgcggcgcga ctgcctgcct ggtactcaac 240

ctcttctgcg cggacctgct cttcatcagc gctatccctc tggtgctggc cgtgcgctgg 300

actgaggcct ggctgctggg ccccgttgcc tgccacctgc tcttctacgt gatgaccctg 360

agcggcagcg tcaccatcct cacgctggcc gcggtcagcc tggagcgcat ggtgtgcatc 420

gtgcacctgc agcgcggcgt gcggggtcct gggcggcggg cgcgggcagt gctgctggcg 480

ctcatctggg gctattcggc ggtcgccgct ctgcctctct gcgtcttctt tcgagtcgtc 540

ccgcaacggc tccccggcgc cgaccaggaa atttcgattt gcacactgat ttggcccacc 600

attcctggag agatctcgtg ggatgtctct tttgttactt tgaacttctt ggtgccagga 660

ctggtcattg tgatcagtta ctccaaaatt ttacagatca caaaggcatc aaggaagagg 720

ctcacggtaa gcctggccta ctcggagagc caccagatcc gcgtgtccca gcaggacttc 780

cggctcttcc gcaccctctt cctcctcatg gtctccttct tcatcatgtg gagccccatc 840

ttcatcacca tcctcctcat cctgatccag aacttcaagc aagacctggt catctggccg 900

tccctcttct tctgggtggt ggccttcaca tttgctaatt cagccctaaa ccccatcctc 960

tacaacatga cactgtgcag gaatgagtgg aagaaaattt tttgctgctt ctggttccca 1020

gaaaagggag ccattttaac agacacatct gtcaaaagaa atgacttgtc gattatttct 1080

ggctaa 1086

<210> 79
<211> 361
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 79

Met Ser Pro Glu Cys Ala Arg Ala Ala Gly Asp Ala Pro Leu Arg Ser
1 5 10 15

Leu Glu Gln Ala Asn Arg Thr Arg Phe Pro Phe Phe Ser Asp Val Lys
20 25 30

Gly Asp His Arg Leu Val Leu Ala Ala Val Glu Thr Thr Val Leu Val
35 40 45

Leu Ile Phe Ala Val Ser Leu Leu Gly Asn Val Cys Ala Leu Val Leu
50 55 60

Val Ala Arg Arg Arg Arg Arg Gly Ala Thr Ala Cys Leu Val Leu Asn
65 70 75 80

Leu Phe Cys Ala Asp Leu Leu Phe Ile Ser Ala Ile Pro Leu Val Leu
85 90 95

Ala Val Arg Trp Thr Glu Ala Trp Leu Leu Gly Pro Val Ala Cys His
100 105 110

Leu Leu Phe Tyr Val Met Thr Leu Ser Gly Ser Val Thr Ile Leu Thr
115 120 125

Leu Ala Ala Val Ser Leu Glu Arg Met Val Cys Ile Val His Leu Gln
130 135 140

Arg Gly Val Arg Gly Pro Gly Arg Arg Ala Arg Ala Val Leu Leu Ala
145 150 155 160

Leu Ile Trp Gly Tyr Ser Ala Val Ala Ala Leu Pro Leu Cys Val Phe

```
                165                 170                 175

Phe Arg Val Val Pro Gln Arg Leu Pro Gly Ala Asp Gln Glu Ile Ser
            180                 185                 190

Ile Cys Thr Leu Ile Trp Pro Thr Ile Pro Gly Glu Ile Ser Trp Asp
        195                 200                 205

Val Ser Phe Val Thr Leu Asn Phe Leu Val Pro Gly Leu Val Ile Val
    210                 215                 220

Ile Ser Tyr Ser Lys Ile Leu Gln Ile Thr Lys Ala Ser Arg Lys Arg
225                 230                 235                 240

Leu Thr Val Ser Leu Ala Tyr Ser Glu Ser His Gln Ile Arg Val Ser
                245                 250                 255

Gln Gln Asp Phe Arg Leu Phe Arg Thr Leu Phe Leu Leu Met Val Ser
            260                 265                 270

Phe Phe Ile Met Trp Ser Pro Ile Phe Ile Thr Ile Leu Leu Ile Leu
        275                 280                 285

Ile Gln Asn Phe Lys Gln Asp Leu Val Ile Trp Pro Ser Leu Phe Phe
    290                 295                 300

Trp Val Val Ala Phe Thr Phe Ala Asn Ser Ala Leu Asn Pro Ile Leu
305                 310                 315                 320

Tyr Asn Met Thr Leu Cys Arg Asn Glu Trp Lys Lys Ile Phe Cys Cys
                325                 330                 335

Phe Trp Phe Pro Glu Lys Gly Ala Ile Leu Thr Asp Thr Ser Val Lys
            340                 345                 350

Arg Asn Asp Leu Ser Ile Ile Ser Gly
        355                 360
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<210> 80
<211> 1086
<212> DNA
<213> Unknown

<220>

<223> Novel Sequence

<400> 80
atgtcccctg aatgcgcgcg ggcagcgggc gacgcgccct tgcgcagcct ggagcaagcc 60

aaccgcaccc gctttccctt cttctccgac gtcaagggcg accaccggct ggtgctggcc 120

gcggtggaga caaccgtgct ggtgctcatc tttgcagtgt cgctgctggg caacgtgtgc 180

gccctggtgc tggtggcgcg ccgacgacgc cgcggcgcga ctgcctgcct ggtactcaac 240

ctcttctgcg cggacctgct cttcatcagc gctatccctc tggtgctggc cgtgcgctgg 300

actgaggcct ggctgctggg ccccgttgcc tgccacctgc tcttctacgt gatgaccctg 360

agcggcagcg tcaccatcct cacgctggcc gcggtcagcc tgaatcgcat ggtgtgcatc 420

gtgcacctgc agcgcggcgt gcggggtcct gggcggcggg cgcgggcagt gctgctggcg 480

ctcatctggg gctattcggc ggtcgccgct ctgcctctct gcgtcttctt tcgagtcgtc 540

ccgcaacggc tccccggcgc cgaccaggaa atttcgattt gcacactgat ttggcccacc 600

attcctggag agatctcgtg ggatgtctct tttgttactt tgaacttctt ggtgccagga 660

ctggtcattg tgatcagtta ctccaaaatt ttacagatca caaaggcatc aaggaagagg 720

ctcacggtaa gcctggccta ctcggagagc caccagatcc gcgtgtccca gcaggacttc 780

cggctcttcc gcaccctctt cctcctcatg gtctccttct tcatcatgtg gagccccatc 840

atcatcacca tcctcctcat cctgatccag aacttcaagc aagacctggt catctggccg 900

tccctcttct tctgggtggt ggccttcaca tttgctaatt cagccctaaa ccccatcctc 960

tacaacatga cactgtgcag gaatgagtgg aagaaaattt tttgctgctt ctggttccca 1020

gaaaagggag ccattttaac agacacatct gtcaaaagaa atgacttgtc gattatttct 1080

ggctaa 1086

<210> 81
<211> 361
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 81

Met Ser Pro Glu Cys Ala Arg Ala Ala Gly Asp Ala Pro Leu Arg Ser
1 5 10 15

Leu Glu Gln Ala Asn Arg Thr Arg Phe Pro Phe Phe Ser Asp Val Lys

20 25 30

Gly Asp His Arg Leu Val Leu Ala Ala Val Glu Thr Thr Val Leu Val
35 40 45

Leu Ile Phe Ala Val Ser Leu Leu Gly Asn Val Cys Ala Leu Val Leu
50 55 60

Val Ala Arg Arg Arg Arg Arg Gly Ala Thr Ala Cys Leu Val Leu Asn
65 70 75 80

Leu Phe Cys Ala Asp Leu Leu Phe Ile Ser Ala Ile Pro Leu Val Leu
85 90 95

Ala Val Arg Trp Thr Glu Ala Trp Leu Leu Gly Pro Val Ala Cys His
100 105 110

Leu Leu Phe Tyr Val Met Thr Leu Ser Gly Ser Val Thr Ile Leu Thr
115 120 125

Leu Ala Ala Val Ser Leu Asn Arg Met Val Cys Ile Val His Leu Gln
130 135 140

Arg Gly Val Arg Gly Pro Gly Arg Arg Ala Arg Ala Val Leu Leu Ala
145 150 155 160

Leu Ile Trp Gly Tyr Ser Ala Val Ala Ala Leu Pro Leu Cys Val Phe
165 170 175

Phe Arg Val Val Pro Gln Arg Leu Pro Gly Ala Asp Gln Glu Ile Ser
180 185 190

Ile Cys Thr Leu Ile Trp Pro Thr Ile Pro Gly Glu Ile Ser Trp Asp
195 200 205

Val Ser Phe Val Thr Leu Asn Phe Leu Val Pro Gly Leu Val Ile Val
210 215 220

Ile Ser Tyr Ser Lys Ile Leu Gln Ile Thr Lys Ala Ser Arg Lys Arg
225 230 235 240

Leu Thr Val Ser Leu Ala Tyr Ser Glu Ser His Gln Ile Arg Val Ser
245 250 255

Gln Gln Asp Phe Arg Leu Phe Arg Thr Leu Phe Leu Leu Met Val Ser
260 265 270

Phe Phe Ile Met Trp Ser Pro Ile Ile Ile Thr Ile Leu Leu Ile Leu
275 280 285

Ile Gln Asn Phe Lys Gln Asp Leu Val Ile Trp Pro Ser Leu Phe Phe
290 295 300

Trp Val Val Ala Phe Thr Phe Ala Asn Ser Ala Leu Asn Pro Ile Leu
305 310 315 320

Tyr Asn Met Thr Leu Cys Arg Asn Glu Trp Lys Lys Ile Phe Cys Cys
325 330 335

Phe Trp Phe Pro Glu Lys Gly Ala Ile Leu Thr Asp Thr Ser Val Lys
340 345 350

Arg Asn Asp Leu Ser Ile Ile Ser Gly
355 360

<210> 82
<211> 1212
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 82
atggcttgca atggcagtgc ggccaggggg cactttgacc ctgaggactt gaacctgact 60

gacgaggcac tgagactcaa gtacctgggg ccccagcaga cagagctgtt catgcccatc 120

tgtgccacat acctgctgat cttcgtggtg ggcgctgtgg gcaatgggct gacctgtctg 180

gtcatcctgc gccacaaggc catgcgcacg cctaccaact actacctctt cagcctggcc 240

gtgtcggacc tgctggtgct gctggtgggc ctgcccctgg agctctatga gatgtggcac 300

aactaccccc tcctgctggg cgttggtggc tgctatttcc gcacgctact gtttgagatg 360

gtctgcctgg cctcagtgct caacgtcact gccctgagcg tggaacgcta tgtggccgtg 420

gtgcacccac tccaggccag gtccatggtg acgcgggccc atgtgcgccg agtgcttggg 480

gccgtctggg gtcttgccat gctctgctcc ctgcccaaca ccagcctgca cggcatccgg 540

cagctgcacg tgccctgccg gggcccagtg ccagactcag ctgtttgcat gctggtccgc 600

ccacgggccc tctacaacat ggtagtgcag accaccgcgc tgctcttctt ctgcctgccc 660

atggccatca tgagcgtgct ctacctgctc attgggctgc gactgcggcg ggagaggctg 720

ctgctcatgc aggaggccaa gggcaggggc tctgcagcag ccaggtccag atacacctgc 780

aggctccagc agcacgatcg gggccggaga caagtgaaaa agatgctgtt tgtcctggtc 840

gtggtgtttg gcatctgctg ggccccgttc cacgccgacc gcgtcatgtg gagcgtcgtg 900

tcacagtgga cagatggcct gcacctggcc ttccagcacg tgcacgtcat ctccggcatc 960

ttcttctacc tgggctcggc ggccaacccc gtgctctata gcctcatgtc cagccgcttc 1020

cgagagacct tccaggaggc cctgtgcctc ggggcctgct gccatcgcct cagaccccgc 1080

cacagctccc acagcctcag caggatgacc acaggcagca ccctgtgtga tgtgggctcc 1140

ctgggcagct gggtccaccc cctggctggg aacgatggcc cagaggcgca gcaagagacc 1200

gatccatcct ga 1212

<210> 83
<211> 403
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 83

Met Ala Cys Asn Gly Ser Ala Ala Arg Gly His Phe Asp Pro Glu Asp
1 5 10 15

Leu Asn Leu Thr Asp Glu Ala Leu Arg Leu Lys Tyr Leu Gly Pro Gln
20 25 30

Gln Thr Glu Leu Phe Met Pro Ile Cys Ala Thr Tyr Leu Leu Ile Phe
35 40 45

Val Val Gly Ala Val Gly Asn Gly Leu Thr Cys Leu Val Ile Leu Arg
50 55 60

His Lys Ala Met Arg Thr Pro Thr Asn Tyr Tyr Leu Phe Ser Leu Ala
65 70 75 80

Val Ser Asp Leu Leu Val Leu Leu Val Gly Leu Pro Leu Glu Leu Tyr
85 90 95

```
Glu Met Trp His Asn Tyr Pro Phe Leu Leu Gly Val Gly Gly Cys Tyr
            100                 105                 110

Phe Arg Thr Leu Leu Phe Glu Met Val Cys Leu Ala Ser Val Leu Asn
        115                 120                 125

Val Thr Ala Leu Ser Val Glu Arg Tyr Val Ala Val Val His Pro Leu
    130                 135                 140

Gln Ala Arg Ser Met Val Thr Arg Ala His Val Arg Arg Val Leu Gly
145                 150                 155                 160

Ala Val Trp Gly Leu Ala Met Leu Cys Ser Leu Pro Asn Thr Ser Leu
                165                 170                 175

His Gly Ile Arg Gln Leu His Val Pro Cys Arg Gly Pro Val Pro Asp
            180                 185                 190

Ser Ala Val Cys Met Leu Val Arg Pro Arg Ala Leu Tyr Asn Met Val
        195                 200                 205

Val Gln Thr Thr Ala Leu Leu Phe Phe Cys Leu Pro Met Ala Ile Met
    210                 215                 220

Ser Val Leu Tyr Leu Leu Ile Gly Leu Arg Leu Arg Arg Glu Arg Leu
225                 230                 235                 240

Leu Leu Met Gln Glu Ala Lys Gly Arg Gly Ser Ala Ala Ala Arg Ser
                245                 250                 255

Arg Tyr Thr Cys Arg Leu Gln Gln His Asp Arg Gly Arg Arg Gln Val
            260                 265                 270

Lys Lys Met Leu Phe Val Leu Val Val Val Phe Gly Ile Cys Trp Ala
        275                 280                 285

Pro Phe His Ala Asp Arg Val Met Trp Ser Val Val Ser Gln Trp Thr
    290                 295                 300

Asp Gly Leu His Leu Ala Phe Gln His Val His Val Ile Ser Gly Ile
305                 310                 315                 320
```

Phe Phe Tyr Leu Gly Ser Ala Ala Asn Pro Val Leu Tyr Ser Leu Met
325 330 335

Ser Ser Arg Phe Arg Glu Thr Phe Gln Glu Ala Leu Cys Leu Gly Ala
340 345 350

Cys Cys His Arg Leu Arg Pro Arg His Ser Ser His Ser Leu Ser Arg
355 360 365

Met Thr Thr Gly Ser Thr Leu Cys Asp Val Gly Ser Leu Gly Ser Trp
370 375 380

Val His Pro Leu Ala Gly Asn Asp Gly Pro Glu Ala Gln Gln Glu Thr
385 390 395 400

Asp Pro Ser

<210> 84
<211> 930
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 84
atgaatggca cctacaacac ctgtggctcc agcgacctca cctggccccc agcgatcaag 60

ctgggcttct acgcctactt gggcgtcctg ctggtgctag gcctgctgct caacagcctg 120

gcgctctggg tgttctgctg ccgcatgcag cagtggacgg agacccgcat ctacatgacc 180

aacctggcgg tggccgacct ctgcctgctg tgcaccttgc ccttcgtgct gcactccctg 240

cgagacacct cagacacgcc gctgtgccag ctctcccagg gcatctacct gaccaacagg 300

tacatgagca tcagcctggt cacggccatc gccgtggacc gctatgtggc cgtgcggcac 360

ccgctgcgtg cccgcgggct gcggtccccc aggcaggctg cggccgtgtg cgcggtcctc 420

tgggtgctgg tcatcggctc cctggtggct cgctggctcc tggggattca ggagggcggc 480

ttctgcttca ggagcacccg gcacaatttc aactccatgc ggttcccgct gctgggattc 540

tacctgcccc tggccgtggt ggtcttctgc tccctgaagg tggtgactgc cctggcccag 600

aggccaccca ccgacgtggg gcaggcagag gccacccgca aggctaaacg catggtctgg 660

gccaacctcc tggtgttcgt ggtctgcttc ctgcccctgc acgtggggct gacagtgcgc 720

ctcgcagtgg gctggaacgc ctgtgccctc ctggagacga tccgtcgcgc cctgtacata 780

accagcaagc tctcagatgc caactgctgc ctggacgcca tctgctacta ctacatggcc 840

aaggagttcc aggaggcgtc tgcactggcc gtggctcccc gtgctaaggc ccacaaaagc 900

caggactctc tgtgcgtgac cctcgcctaa 930

<210> 85
<211> 309
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 85

Met Asn Gly Thr Tyr Asn Thr Cys Gly Ser Ser Asp Leu Thr Trp Pro
1 5 10 15

Pro Ala Ile Lys Leu Gly Phe Tyr Ala Tyr Leu Gly Val Leu Leu Val
20 25 30

Leu Gly Leu Leu Leu Asn Ser Leu Ala Leu Trp Val Phe Cys Cys Arg
35 40 45

Met Gln Gln Trp Thr Glu Thr Arg Ile Tyr Met Thr Asn Leu Ala Val
50 55 60

Ala Asp Leu Cys Leu Leu Cys Thr Leu Pro Phe Val Leu His Ser Leu
65 70 75 80

Arg Asp Thr Ser Asp Thr Pro Leu Cys Gln Leu Ser Gln Gly Ile Tyr
85 90 95

Leu Thr Asn Arg Tyr Met Ser Ile Ser Leu Val Thr Ala Ile Ala Val
100 105 110

Asp Arg Tyr Val Ala Val Arg His Pro Leu Arg Ala Arg Gly Leu Arg
115 120 125

Ser Pro Arg Gln Ala Ala Ala Val Cys Ala Val Leu Trp Val Leu Val
130 135 140

Ile Gly Ser Leu Val Ala Arg Trp Leu Leu Gly Ile Gln Glu Gly Gly

145 150 155 160

Phe Cys Phe Arg Ser Thr Arg His Asn Phe Asn Ser Met Arg Phe Pro
165 170 175

Leu Leu Gly Phe Tyr Leu Pro Leu Ala Val Val Val Phe Cys Ser Leu
180 185 190

Lys Val Val Thr Ala Leu Ala Gln Arg Pro Pro Thr Asp Val Gly Gln
195 200 205

Ala Glu Ala Thr Arg Lys Ala Lys Arg Met Val Trp Ala Asn Leu Leu
210 215 220

Val Phe Val Val Cys Phe Leu Pro Leu His Val Gly Leu Thr Val Arg
225 230 235 240

Leu Ala Val Gly Trp Asn Ala Cys Ala Leu Leu Glu Thr Ile Arg Arg
245 250 255

Ala Leu Tyr Ile Thr Ser Lys Leu Ser Asp Ala Asn Cys Cys Leu Asp
260 265 270

Ala Ile Cys Tyr Tyr Tyr Met Ala Lys Glu Phe Gln Glu Ala Ser Ala
275 280 285

Leu Ala Val Ala Pro Arg Ala Lys Ala His Lys Ser Gln Asp Ser Leu
290 295 300

Cys Val Thr Leu Ala
305

<210> 86
<211> 1446
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 86
atgcggtggc tgtggcccct ggctgtctct cttgctgtga ttttggctgt ggggctaagc 60

agggtctctg ggggtgcccc cctgcacctg ggcaggcaca gagccgagac ccaggagcag 120

cagagccgat ccaagagggg caccgaggat gaggaggcca agggcgtgca gcagtatgtg 180

cctgaggagt gggcggagta cccccggccc attcaccctg ctggcctgca gccaaccaag 240

cccttggtgg ccaccagccc taaccccgac aaggatgggg gcaccccaga cagtgggcag 300

gaactgaggg gcaatctgac aggggcacca gggcagaggc tacagatcca gaacccccctg 360

tatccggtga ccgagagctc ctacagtgcc tatgccatca tgcttctggc gctggtggtg 420

tttgcggtgg gcattgtggg caacctgtcg gtcatgtgca tcgtgtggca cagctactac 480

ctgaagagcg cctggaactc catccttgcc agcctggccc tctgggattt tctggtcctc 540

tttttctgcc tccctattgt catcttcaac gagatcacca agcagaggct actgggtgac 600

gtttcttgtc gtgccgtgcc cttcatggag gtctcctctc tgggagtcac gactttcagc 660

ctctgtgccc tgggcattga ccgcttccac gtggccacca gcaccctgcc caaggtgagg 720

cccatcgagc ggtgccaatc catcctggcc aagttggctg tcatctgggt gggctccatg 780

acgctggctg tgcctgagct cctgctgtgg cagctggcac aggagcctgc ccccaccatg 840

ggcaccctgg actcatgcat catgaaaccc tcagccagcc tgcccgagtc cctgtattca 900

ctggtgatga cctaccagaa cgcccgcatg tggtggtact ttggctgcta cttctgcctg 960

cccatcctct tcacagtcac ctgccagctg gtgacatggc gggtgcgagg ccctccaggg 1020

aggaagtcag agtgcagggc cagcaagcac gagcagtgtg agagccagct caagagcacc 1080

gtggtgggcc tgaccgtggt ctacgccttc tgcaccctcc cagagaacgt ctgcaacatc 1140

gtggtggcct acctctccac cgagctgacc cgccagaccc tggacctcct gggcctcatc 1200

aaccagttct ccaccttctt caagggcgcc atcaccccag tgctgctcct ttgcatctgc 1260

aggccgctgg gccaggcctt cctggactgc tgctgctgct gctgctgtga ggagtgcggc 1320

ggggcttcgg aggcctctgc tgccaatggg tcggacaaca agctcaagac cgaggtgtcc 1380

tcttccatct acttccacaa gcccagggag tcacccccac tcctgccct gggcacacct 1440

tgctga 1446

<210> 87
<211> 481
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 87

Met Arg Trp Leu Trp Pro Leu Ala Val Ser Leu Ala Val Ile Leu Ala

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1               5                   10                  15

Val Gly Leu Ser Arg Val Ser Gly Gly Ala Pro Leu His Leu Gly Arg
            20                  25                  30

His Arg Ala Glu Thr Gln Glu Gln Gln Ser Arg Ser Lys Arg Gly Thr
        35                  40                  45

Glu Asp Glu Glu Ala Lys Gly Val Gln Gln Tyr Val Pro Glu Glu Trp
    50                  55                  60

Ala Glu Tyr Pro Arg Pro Ile His Pro Ala Gly Leu Gln Pro Thr Lys
65                  70                  75                  80

Pro Leu Val Ala Thr Ser Pro Asn Pro Asp Lys Asp Gly Gly Thr Pro
                85                  90                  95

Asp Ser Gly Gln Glu Leu Arg Gly Asn Leu Thr Gly Ala Pro Gly Gln
            100                 105                 110

Arg Leu Gln Ile Gln Asn Pro Leu Tyr Pro Val Thr Glu Ser Ser Tyr
        115                 120                 125

Ser Ala Tyr Ala Ile Met Leu Leu Ala Leu Val Val Phe Ala Val Gly
    130                 135                 140

Ile Val Gly Asn Leu Ser Val Met Cys Ile Val Trp His Ser Tyr Tyr
145                 150                 155                 160

Leu Lys Ser Ala Trp Asn Ser Ile Leu Ala Ser Leu Ala Leu Trp Asp
                165                 170                 175

Phe Leu Val Leu Phe Phe Cys Leu Pro Ile Val Ile Phe Asn Glu Ile
            180                 185                 190

Thr Lys Gln Arg Leu Leu Gly Asp Val Ser Cys Arg Ala Val Pro Phe
        195                 200                 205

Met Glu Val Ser Ser Leu Gly Val Thr Thr Phe Ser Leu Cys Ala Leu
    210                 215                 220

Gly Ile Asp Arg Phe His Val Ala Thr Ser Thr Leu Pro Lys Val Arg
225                 230                 235                 240
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Pro Ile Glu Arg Cys Gln Ser Ile Leu Ala Lys Leu Ala Val Ile Trp
                245                 250                 255

Val Gly Ser Met Thr Leu Ala Val Pro Glu Leu Leu Leu Trp Gln Leu
            260                 265                 270

Ala Gln Glu Pro Ala Pro Thr Met Gly Thr Leu Asp Ser Cys Ile Met
        275                 280                 285

Lys Pro Ser Ala Ser Leu Pro Glu Ser Leu Tyr Ser Leu Val Met Thr
    290                 295                 300

Tyr Gln Asn Ala Arg Met Trp Trp Tyr Phe Gly Cys Tyr Phe Cys Leu
305                 310                 315                 320

Pro Ile Leu Phe Thr Val Thr Cys Gln Leu Val Thr Trp Arg Val Arg
                325                 330                 335

Gly Pro Pro Gly Arg Lys Ser Glu Cys Arg Ala Ser Lys His Glu Gln
            340                 345                 350

Cys Glu Ser Gln Leu Lys Ser Thr Val Val Gly Leu Thr Val Val Tyr
        355                 360                 365

Ala Phe Cys Thr Leu Pro Glu Asn Val Cys Asn Ile Val Val Ala Tyr
    370                 375                 380

Leu Ser Thr Glu Leu Thr Arg Gln Thr Leu Asp Leu Leu Gly Leu Ile
385                 390                 395                 400

Asn Gln Phe Ser Thr Phe Phe Lys Gly Ala Ile Thr Pro Val Leu Leu
                405                 410                 415

Leu Cys Ile Cys Arg Pro Leu Gly Gln Ala Phe Leu Asp Cys Cys Cys
            420                 425                 430

Cys Cys Cys Cys Glu Glu Cys Gly Gly Ala Ser Glu Ala Ser Ala Ala
        435                 440                 445

Asn Gly Ser Asp Asn Lys Leu Lys Thr Glu Val Ser Ser Ser Ile Tyr
    450                 455                 460
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Phe His Lys Pro Arg Glu Ser Pro Pro Leu Leu Pro Leu Gly Thr Pro
465 470 475 480

Cys

<210> 88
<211> 6
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 88

Thr Leu Glu Ser Ile Met
1 5

<210> 89
<211> 5
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 89

Glu Tyr Asn Leu Val
1 5

<210> 90
<211> 5
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 90

Asp Cys Gly Leu Phe
1 5

<210> 91
<211> 34
<212> DNA
<213> Unknown

<220>

<223> Novel Sequence

<400> 91
gatcaagctt ccatggcgtg ctgcctgagc gagg 34

<210> 92
<211> 53
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 92
gatcggatcc ttagaacagg ccgcagtcct tcaggttcag ctgcaggatg gtg 53

<210> 93
<211> 5
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 93

Gln Tyr Glu Leu Leu
1 5

<210> 94
<211> 5
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 94

Asp Cys Gly Leu Phe
1 5

<210> 95
<211> 1185
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 95
atgggctgcc tcggcaacag taagaccgag gaccagcgca acgaggagaa ggcgcagcgc 60

gaggccaaca aaaagatcga gaagcagctg cagaaggaca agcaggtcta ccgggccacg 120

caccgcctgc tgctgctggg tgctggagag tctggcaaaa gcaccattgt gaagcagatg 180

aggatcctac atgttaatgg gtttaacgga gagggcggcg aagaggaccc gcaggctgca 240

aggagcaaca gcgatggtga gaaggccacc aaagtgcagg acatcaaaaa caacctgaag 300

gaggccattg aaaccattgt ggccgccatg agcaacctgg tgccccccgt ggagctggcc 360

aaccctgaga accagttcag agtggactac attctgagcg tgatgaacgt gccaaacttt 420

gacttcccac ctgaattcta tgagcatgcc aaggctctgt gggaggatga gggagttcgt 480

gcctgctacg agcgctccaa cgagtaccag ctgatcgact gtgcccagta cttcctggac 540

aagattgatg tgatcaagca ggccgactac gtgccaagtg accaggacct gcttcgctgc 600

cgcgtcctga cctctggaat ctttgagacc aagttccagg tggacaaagt caacttccac 660

atgttcgatg tgggcggcca gcgcgatgaa cgccgcaagt ggatccagtg cttcaatgat 720

gtgactgcca tcatcttcgt ggtggccagc agcagctaca acatggtcat ccgggaggac 780

aaccagacca accgtctgca ggaggctctg aacctcttca agagcatctg gaacaacaga 840

tggctgcgta ccatctctgt gatcctcttc ctcaacaagc aagatctgct tgctgagaag 900

gtcctcgctg ggaaatcgaa gattgaggac tactttccag agttcgctcg ctacaccact 960

cctgaggatg cgactcccga gcccggagag gacccacgcg tgacccgggc caagtacttc 1020

atccgggatg agtttctgag aatcagcact gctagtggag atggacgtca ctactgctac 1080

cctcacttta cctgcgccgt ggacactgag aacatccgcc gtgtcttcaa cgactgccgt 1140

gacatcatcc agcgcatgca tcttcgcgac tgcgggctgt tttaa 1185

<210> 96
<211> 393
<212> PRT
<213> Unknown

<220>
<223> Novel Sequence

<400> 96

Met Gly Cys Leu Gly Asn Ser Lys Thr Glu Asp Gln Arg Asn Glu Glu
1 5 10 15

Lys Ala Gln Arg Glu Ala Asn Lys Lys Ile Glu Lys Gln Leu Gln Lys
20 25 30

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Asp Lys Gln Val Tyr Arg Ala Thr His Arg Leu Leu Leu Leu Gly Ala
        35                  40                  45

Gly Glu Ser Gly Lys Ser Thr Ile Val Lys Gln Met Arg Ile Leu His
    50                  55                  60

Val Asn Gly Phe Asn Gly Glu Gly Gly Glu Glu Asp Pro Gln Ala Ala
65                  70                  75                  80

Arg Ser Asn Ser Asp Gly Glu Lys Ala Thr Lys Val Gln Asp Ile Lys
                85                  90                  95

Asn Asn Leu Lys Glu Ala Ile Glu Thr Ile Val Ala Ala Ser Asn Leu
            100                 105                 110

Val Pro Pro Val Glu Leu Ala Asn Pro Glu Asn Gln Phe Arg Val Asp
        115                 120                 125

Tyr Ile Leu Ser Val Met Asn Val Pro Asn Phe Asp Phe Pro Pro Glu
    130                 135                 140

Phe Tyr Glu His Ala Lys Ala Leu Trp Glu Asp Glu Gly Val Arg Ala
145                 150                 155                 160

Cys Tyr Glu Arg Ser Asn Glu Tyr Gln Leu Ile Asp Cys Ala Gln Tyr
                165                 170                 175

Phe Leu Asp Lys Ile Asp Val Ile Lys Gln Ala Asp Tyr Val Pro Ser
            180                 185                 190

Asp Gln Asp Leu Leu Arg Cys Arg Val Leu Thr Ser Gly Ile Phe Glu
        195                 200                 205

Thr Lys Phe Gln Val Asp Lys Val Asn Phe His Met Phe Asp Val Gly
    210                 215                 220

Gly Gln Arg Asp Glu Arg Arg Lys Trp Ile Gln Cys Phe Asn Asp Val
225                 230                 235                 240

Thr Ala Ile Ile Phe Val Val Ala Ser Ser Ser Tyr Asn Met Val Ile
                245                 250                 255

Arg Glu Asp Asn Gln Thr Asn Arg Leu Gln Glu Ala Leu Asn Leu Phe
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260 265 270

Lys Ser Ile Trp Asn Asn Arg Trp Leu Arg Thr Ile Ser Val Ile Leu
275 280 285

Phe Leu Asn Lys Gln Asp Leu Leu Ala Glu Lys Val Leu Ala Gly Lys
290 295 300

Ser Lys Ile Glu Asp Tyr Phe Pro Glu Phe Ala Arg Tyr Thr Thr Pro
305 310 315 320

Glu Asp Ala Thr Pro Glu Pro Gly Glu Asp Pro Arg Val Thr Arg Ala
325 330 335

Lys Tyr Phe Ile Arg Asp Glu Phe Leu Arg Ile Ser Thr Ala Ser Gly
340 345 350

Asp Gly Arg His Tyr Cys Tyr Pro His Phe Thr Cys Ala Val Asp Thr
355 360 365

Glu Asn Ile Arg Arg Val Phe Asn Asp Cys Arg Asp Ile Ile Gln Arg
370 375 380

Met His Leu Arg Asp Cys Gly Leu Phe
385 390

<210> 97
<211> 1014
<212> DNA
<213> Homo sapiens

<400> 97
atgaactcgt gggacgcggg cctggcgggg ctactggtgg gcacgatggg cgtctcgctg 60

ctgtccaacg cgctggtgct gctctgcctg ctgcacagcg cggacatccg ccgccaggcg 120

ccggcgctct tcaccctgaa cctcacgtgc gggaacctgc tgtgcaccgt ggtcaacatg 180

ccgctcacgc tggccggcgt cgtggcgcag cggcagccgg cgggcgaccg cctgtgccgc 240

ctggctgcct tcctcgacac cttcctggct gccaactcca tgctcagcat ggccgcgctc 300

agcatcgacc gctgggtggc cgtggtcttc ccgctgagct accgggccaa gatgccgcct 360

ccgagatgcg cgctcatcct ggcctacacg tggctgcacg cgctcacctt cccagccgcc 420

gcgctcgccc tgtcctggct cggcttccac cagctgtacg cctcgtgcac gctgtgcagc 480

cggcggccgg acgagcgcct gcgcttcgcc gtattcactg gcgccttcca cgctctcagc 540

ttcctgctct ccttcgtcgt gctctgctgc acgtacctca aggtgctcaa ggtggcccgc 600

ttccattgca agcgcatcga cgtgatcacc atgcagacgc tcgtgctgct ggtggacctg 660

caccccagtg tgcgggaacg ctgtctggag gagcagaagc ggaggcgaca gcgagccacc 720

aagaagatca gcaccttcat agggaccttc cttgtgtgct tcgcgcccta tgtgatcacc 780

aggctagtgg agctcttctc cacggtgccc atcggctccc actgggggt gctgtccaag 840

tgcttggcgt acagcaaggc cgcatccgac ccctttgtgt actccttact gcgacaccag 900

taccgcaaaa gctgcaagga gattctgaac aggctcctgc acagacgctc catccactcc 960

tctggcctca caggcgactc tcacagccag aacattctgc cggtgtctga gtga 1014

<210> 98
<211> 337
<212> PRT
<213> Homo sapiens

<400> 98

Met Asn Ser Trp Asp Ala Gly Leu Ala Gly Leu Leu Val Gly Thr Met
1 5 10 15

Gly Val Ser Leu Leu Ser Asn Ala Leu Val Leu Leu Cys Leu Leu His
20 25 30

Ser Ala Asp Ile Arg Arg Gln Ala Pro Ala Leu Phe Thr Leu Asn Leu
35 40 45

Thr Cys Gly Asn Leu Leu Cys Thr Val Val Asn Met Pro Leu Thr Leu
50 55 60

Ala Gly Val Val Ala Gln Arg Gln Pro Ala Gly Asp Arg Leu Cys Arg
65 70 75 80

Leu Ala Ala Phe Leu Asp Thr Phe Leu Ala Ala Asn Ser Met Leu Ser
85 90 95

Met Ala Ala Leu Ser Ile Asp Arg Trp Val Ala Val Val Phe Pro Leu
100 105 110

Ser Tyr Arg Ala Lys Met Pro Pro Pro Arg Cys Ala Leu Ile Leu Ala
115 120 125

Tyr Thr Trp Leu His Ala Leu Thr Phe Pro Ala Ala Ala Leu Ala Leu
130 135 140

Ser Trp Leu Gly Phe His Gln Leu Tyr Ala Ser Cys Thr Leu Cys Ser
145 150 155 160

Arg Arg Pro Asp Glu Arg Leu Arg Phe Ala Val Phe Thr Gly Ala Phe
165 170 175

His Ala Leu Ser Phe Leu Leu Ser Phe Val Val Leu Cys Cys Thr Tyr
180 185 190

Leu Lys Val Leu Lys Val Ala Arg Phe His Cys Lys Arg Ile Asp Val
195 200 205

Ile Thr Met Gln Thr Leu Val Leu Leu Val Asp Leu His Pro Ser Val
210 215 220

Arg Glu Arg Cys Leu Glu Glu Gln Lys Arg Arg Arg Gln Arg Ala Thr
225 230 235 240

Lys Lys Ile Ser Thr Phe Ile Gly Thr Phe Leu Val Cys Phe Ala Pro
245 250 255

Tyr Val Ile Thr Arg Leu Val Glu Leu Phe Ser Thr Val Pro Ile Gly
260 265 270

Ser His Trp Gly Val Leu Ser Lys Cys Leu Ala Tyr Ser Lys Ala Ala
275 280 285

Ser Asp Pro Phe Val Tyr Ser Leu Leu Arg His Gln Tyr Arg Lys Ser
290 295 300

Cys Lys Glu Ile Leu Asn Arg Leu Leu His Arg Arg Ser Ile His Ser
305 310 315 320

Ser Gly Leu Thr Gly Asp Ser His Ser Gln Asn Ile Leu Pro Val Ser
325 330 335

Glu

<210> 99
<211> 21
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 99
cgagaaggtg ctcaaggtgg c 21

<210> 100
<211> 30
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 100
gagaagagct ccactagcct ggtgatcaca 30

<210> 101
<211> 36
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 101
gaattcatga actcgtggga cgcgggcctg gcgggc 36

<210> 102
<211> 32
<212> DNA
<213> Unknown

<220>
<223> Novel Sequence

<400> 102
ctcgagtcac tcagacaccg gcagaatgtt ct 32